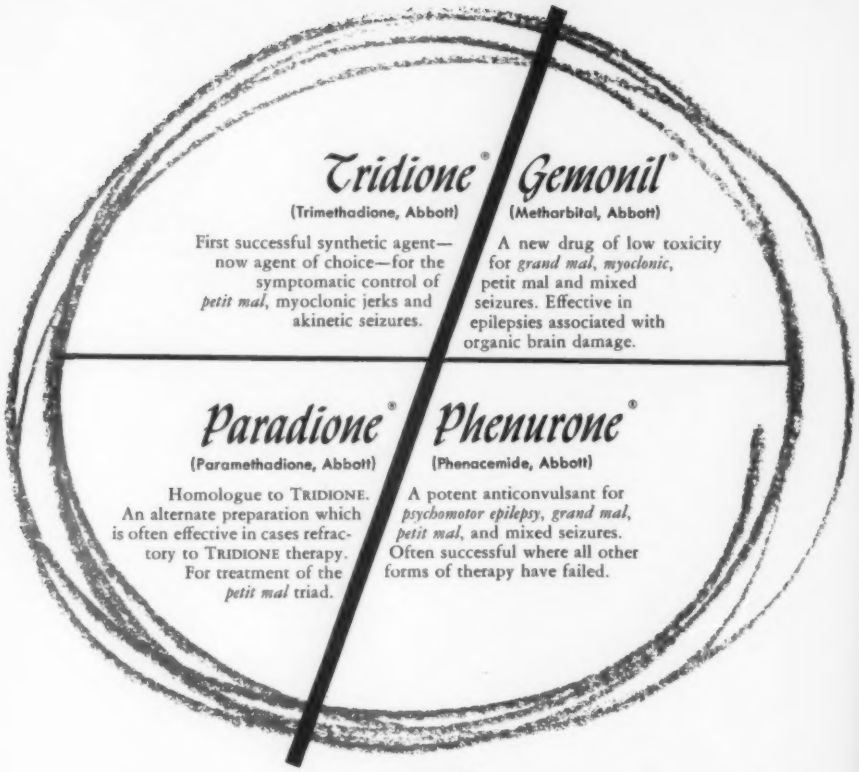
Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

JANUARY--1954

Volume 4—Number 1


Tridione®
(Trimethadione, Abbott)
First successful synthetic agent—now agent of choice—for the symptomatic control of *petit mal*, myoclonic jerks and akinetic seizures.
Gemonil®
(Metharbital, Abbott)
A new drug of low toxicity for *grand mal*, *myoclonic*, petit mal and mixed seizures. Effective in epilepsies associated with organic brain damage.
Paradione®
(Paramethadione, Abbott)
Homologue to TRIDIONE. An alternate preparation which is often effective in cases refractory to TRIDIONE therapy. For treatment of the *petit mal* triad.
Phenurone®
(Phenacemide, Abbott)
A potent anticonvulsant for *psychomotor epilepsy*, *grand mal*, *petit mal*, and mixed seizures. Often successful where all other forms of therapy have failed.

WHY *Four* DRUGS FOR EPILEPSY?

REMEMBER when bromides were the first and last resource of antiepileptic medicine? Hope and doubt were never too far apart. Today you may *choose* your weapon, add or alternate drugs, *individualize* your treatment. Above are four modern anticonvulsants, eminently useful in a variety of seizure types. Each has specific uses, advantages. All are abundantly documented. Remember them. Use them, wisely and carefully. But—please—before you prescribe any of these drugs, write for literature.

Abbott Laboratories, North Chicago, Illinois. Abbott

182

Neurology

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

VOLUME IV

JANUARY 1954 – DECEMBER 1954

LANCET PUBLICATIONS, INCORPORATED
MINNEAPOLIS, MINNESOTA

Neurology

OFFICIAL JOURNAL
OF THE
AMERICAN ACADEMY
OF
NEUROLOGY

BOARD OF EDITORS

Editor-in-Chief:

RUSSELL N. DEJONG, M.D., *Ann Arbor, Michigan*

Associate Editor:

MABEL G. MASTEN, M.D., *Miami, Florida*

Editorial Board:

RAYMOND D. ADAMS, M.D., *Boston, Massachusetts*

PEARCE BAILEY, M.D., *Washington, D. C.*

FRANCIS M. FORSTER, M.D., *Washington, D. C.*

ROLAND P. MACKAY, *Chicago, Illinois*

H. HOUSTON MERRITT, *New York, New York*

RICHARD B. RICHTER, M.D., *Chicago, Illinois*

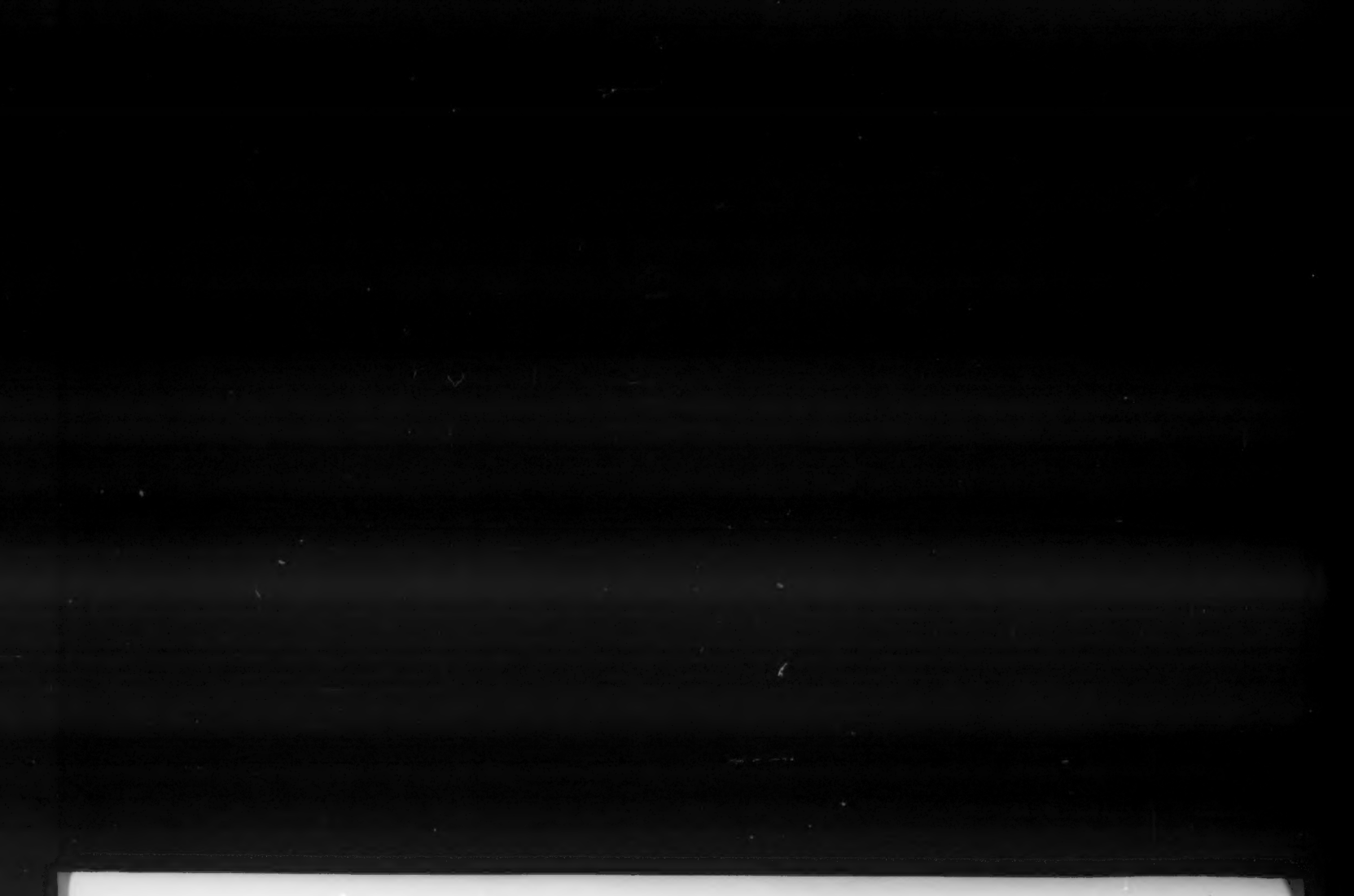
AUGUSTUS S. ROSE, M.D., *Los Angeles, California*

ALPHONSE R. VONDERAHE, M.D., *Cincinnati, Ohio*

A. EARL WALKER, M.D., *Baltimore, Maryland*

ROBERT WARTENBERG, M.D., *San Francisco, California*

PAUL I. YAKOVLEV, M.D., *Boston, Massachusetts*



better control for the majority of diabetics . . .

NPH INSULIN

NPH Iletin

(Insulin, Lilly)

a moderately long-acting Insulin, is a carefully standardized preparation of this type

FOR INTERMEDIATE EFFECT: (affords best control for most patients) NPH Iletin (Insulin, Lilly), U-40 and U-80

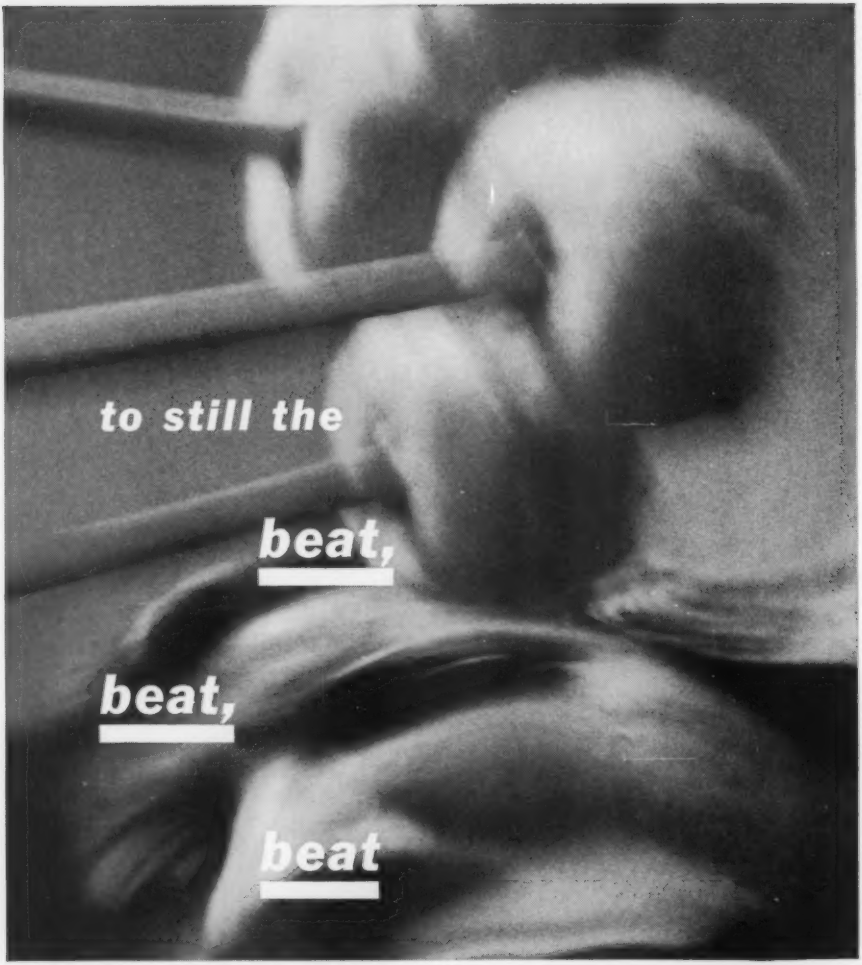
FOR RAPID EFFECT: Iletin (Insulin, Lilly), U-40, U-80, and U-100. Iletin (Insulin, Lilly) made from Zinc-Insulin Crystals, U-40 and U-80

FOR PROLONGED EFFECT: Protamine, Zinc & Iletin (Insulin, Lilly)—Protamine Zinc Insulin—U-40 and U-80

IN 10-CC. VIALS

Lilly QUALITY / RESEARCH / INTEGRITY

ELI LILLY AND COMPANY, INDIANAPOLIS 6, INDIANA, U. S. A.



of ever-mounting tensions and irritations

Here is an effective aid for your tense and nervous patient who has poor appetite. Bēplete provides low-dosage sedation and therapeutic vitamins (including substantial quantities of vitamin B_{12}).

Bēplete®

Vitamins B-Complex with Phenobarbital

ELIXIR TABLETS

Also available: Bēplete with Belladonna; Elixir and Capsules

PHILADELPHIA 2, PA. Wyeth®

Neurology

OFFICIAL JOURNAL
OF THE
AMERICAN ACADEMY
OF
NEUROLOGY

BOARD OF EDITORS

Editor-in-Chief:

RUSSELL N. DEJONG, M.D., *Ann Arbor, Michigan*

Associate Editor:

WEBB HAYMAKER, M.D., *Washington, D.C.*

Editorial Board:

RAYMOND D. ADAMS, M.D., *Boston, Massachusetts*

PEARCE BAILEY, M.D., *Washington, D. C.*

DOUGLAS N. BUCHANAN, M.D., *Chicago, Illinois*

FRANCIS M. FORSTER, M.D., *Washington, D. C.*

MABEL G. MASTEN, M.D., *Madison, Wisconsin*

RICHARD B. RICHTER, M.D., *Chicago, Illinois*

AUGUSTUS S. ROSE, M.D., *Los Angeles, California*

ALPHONSE R. VONDERAHE, M.D., *Cincinnati, Ohio*

A. EARL WALKER, M.D., *Baltimore, Maryland*

ROBERT WARTENBERG, M.D., *San Francisco, California*

PAUL I. YAKOVLEV, M.D., *Boston, Massachusetts*

NEUROLOGY is published monthly at 84 South Tenth Street, Minneapolis 3, Minnesota, by LANCET PUBLICATIONS, INC. Subscription rate: $12.00 a year, $1.00 a copy; outside U.S. $13.00 a year, $1.10 a copy. Entered as second class matter at the postoffice at Minneapolis, Jan. 23, 1951.

In the Treatment of

NEURITIS

(Sciatic—Intercostal—Facial)

"...patients responded with complete relief of pain"*

WITH PROTAMIDE

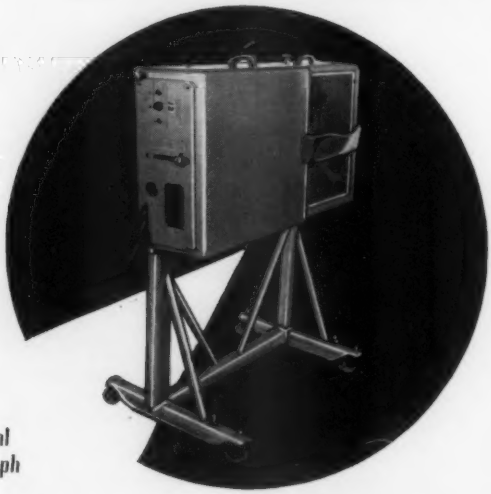
Richard T. Smith, M.D., in a currently published paper, "Treatment of Neuritis with Protamide" reports: 84 patients of 104 had complete relief of pain in sciatic, intercostal and facial neuritis with one daily injection of Protamide for five or ten days. "... 49 were discharged as cured after five days of therapy." No intolerance to Protamide, systemic or local was found in the 125 patients (104 plus 21 controls). Two qualifications for practical application of this study are:

1. *The elimination of cases due to mechanical pressure.*
2. *Early treatment after onset.*

Your prescription blank marked NEURITIS REPRINT will bring literature.

SHERMAN LABORATORIES
BIOLOGICALS • PHARMACEUTICALS
WINDSOR DETROIT 11, MICH. LOS ANGELES

Automatically controlled SERIAL ANGIOGRAPHY



Model 110 Universal Automatic Seriograph

Here is automatically controlled serial angiography with highest quality, standard size pictures and standard developing procedures!

Full control by Radiologist permits test pictures and delays during picture cycle. The 12 individual cassettes, each with its own set of screens, give you 11″ x 14″ (or smaller) standard pictures for adult angiographic studies.

Seriograph operation is equally efficient in the horizontal or vertical position with simple change-over. Automatic time selector gives ½ to 2 second infinitely variable interval.

For details of these and many other outstanding features of the new Model 110 Universal Automatic Seriograph write to:

THE *Automatic* SERIOGRAPH CORPORATION

4910 CALVERT ROAD • COLLEGE PARK • MARYLAND

GRASS INSTRUMENT CO.

101 OLD COLONY AVE.
QUINCY, MASS.
P123-0002

SPECIFY
A GRASS MODEL III SERIES ELECTROENCEPHALOGRAPH

THE INSTRUMENT PROVEN BY
THE MOST FAMOUS HOSPITALS, UNIVERSITIES, AND CLINICS
THROUGHOUT THE WORLD
FOR
ACCURACY
DEPENDABILITY
ECONOMY
CONVENIENCE
EXPANDABILITY

MAKERS OF ELECTROENCEPHALOGRAPHS AND
ELECTROPHYSIOLOGICAL INSTRUMENTS SINCE 1935

Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

Volume 4, Number 1

Contents • JANUARY, 1954

Role of the Brainstem in Blood Pressure Regulation in the Dog
J. D. MC QUEEN, M.D., KENNETH M. BROWNE, M.D. AND A. EARL WALKER, M.D. 1

Some Innovations in Human Stereoencephalotomy
JOSÉ M. R. DELGADO, M.D., HANNIBAL HAMLIN, M.D. AND DONALD J. NALEBUFF, D.M.D. 14

Acquired Epilepsy – A Study of 535 Cases
BUSHNELL SMITH, M.D., GEOFFREY C. ROBINSON, M.D. AND WILLIAM G. LENNOX, M.D. 19

Effects of Vasodilatation on Electroencephalograms of Unanesthetized Humans
A. MORELLO, M.D., S. MERLIS, M.D. AND I. S. COOPER, M.D. 29

Clinical Evaluation of Pagitane Hydrochloride in Parkinsonism
ROBERT S. DOW, M.D. AND GORDON N. SMITH, M.D. 33

Amyotrophic Familial Spastic Paraplegia
SIGVALD REFSUM, M.D. AND S. A. SKILLICORN, M.D. 40

Stimulation of the Amygdaloid Nuclear Complex in Unanesthetized Cats
BIRGER R. KAADA, M.D., PER ANDERSON AND JAN JANSEN, JR. 48

NEUROLOGY, copyright 1954 by LANCET PUBLICATIONS, INCORPORATED.® Title registered United States Patent Office. Louis M. Cohen, Publisher. Margaret M. Kane, Managing Editor. Maurice Wolff, Business Manager. 84 South Tenth Street, Minneapolis 3, Minnesota.

ADVERTISING REPRESENTATIVES: *New York 17:* Harrison Rollins, Lee Klemmer, Bernard A. Smiler, George Doyle, John Winter, 50 East 42nd Street. Telephone: Murray Hill 2-8717. *Chicago 6:* Jay H. Herz, 20 North Wacker Drive, Suite 1921. Telephone: Central 6-4619. *San Francisco 4:* Duncan A. Scott & Co., Mills Building. Telephone: Garfield 1-7930. *Los Angeles 5:* Duncan A. Scott & Co., 2978 Wilshire Blvd. Telephone Dunkirk 8-4151.

®JOURNAL-LANCET, GERIATRICS, NEUROLOGY.

PHOTOGRAPH BY VICTOR KEPPLER

Steadies the palsied grip . . .

RABELLON®

COMPOUND OF BELLADONNA ALKALOIDS

Your patient will appreciate the prompt symptomatic relief RABELLON provides in parkinsonism or paralysis agitans.

One week's treatment reduces peripheral tremor, improves muscular coordination, helps control salivation. The patient finds it easier to walk, rise from a chair, lace his shoes. "Consequently his mental outlook often improves."[1]

Quick Information: RABELLON provides synergistic effect of three alkaloids in combination. Each tablet contains hyoscyamine hydrobromide 0.4507 mg., atropine sulfate 0.0372 mg. and scopolamine hydrobromide 0.0119 mg. Quarter-sected tablets, in bottles of 100 and 1000 for convenient administration. Dosage from ¼ to 1¼ tablets, 3 times a day, in the average case. Dosage schedule in package circular.

REFERENCE: 1. Postgrad. Med. 9:65, 1951.

Contents —*Continued*

Cerebral Angiography in Carotid Cavernous Communications
THOMAS C. PARSONS, M.D., EMANUEL J. GULLER, M.D., HAROLD G. WOLFF, M.D. AND HOWARD S. DUNBAR, M.D. 65

Clinico-Therapeutic Discussion
Acute Generalized Muscular Weakness in an Eleven Year Old Girl
J. SLOAN BERRYMAN, M.D., DOUGLAS N. BUCHANAN, M.D., ROBERT S. SCHWAB, M.D. AND LEE M. EATON, M.D. 69

Clinical Pathologic Conference
Presented by H. HOUSTON MERRITT, M.D. AND ABNER WOLF, M.D. 73

Case Report
Traumatic Pneumocrania and Subdural Spinal Fluid
ARDIS STORM-MATHISEN, M.D. 78

INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

Manuscripts submitted for publication (other than those read at meetings of the Academy) should be sent to Dr. Russell N. DeJong, University Hospital, Ann Arbor, Michigan. Books for review and business correspondence should be addressed to NEUROLOGY, 84 South Tenth Street, Minneapolis 3, Minnesota. Articles dealing with the history of neurology should be sent to Dr. Webb Haymaker, Armed Forces Institute of Pathology, 7th and Independence, S.W., Washington 25, D.C. News items related to the American Academy of Neurology or to the field of neurology in general are to be sent to Dr. Pearce Bailey, 4725 Sedgwick, N.W., Washington 16, D.C.

Manuscripts are accepted for publication on condition that they are contributed solely to NEUROLOGY They must be typewritten, double spaced, and only the original copy should be submitted. Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be glossy prints. Tables should be typed on separate sheets. The title of the article, name of author and number of figure should be placed on the back of every illustration, and the top should be designated. Legends for figures should be typed and are not to be attached to the illustrations. If the number of illustrations or tables is excessive, the author will be asked to defray a part of the cost.

References should be designated in the text by superior number, and should be listed at the end of the article in numerical sequence. They should be typed in the following manner:

Journal reference: 1. Franklin, C. R., and Brickner, R. M.: Vasospasm associated with multiple sclerosis, Arch. Neurol. & Psychiat. 58:125, 1947.

Textbook reference: 2. Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 3, Philadelphia, W. B. Saunders Company, 1935, pp. 194-199.

Abbreviations should follow the style of the Quarterly Cumulative Index Medicus.

Galley proofs will be sent to authors for prompt correction. There will be no charge for corrections unless excessive alterations are made. A schedule of charges for reprints will accompany the galley proof.

"look to
LEKTRA
for the finest
in electronic
equipment"

Electro-Shock Therapy with proven GLISSANDO TREATMENT

reduces severity of convulsion . . .
reduces chance of fracture . . .

Model 160-G
$250.00
As illustrated complete with electrodes

Model 302-G
$395.00
As illustrated complete with electrodes

PORTABLE UNITS

Glissando in Electro Shock Therapy is the method of applying the shock stimulus to the patient in a smooth, gradually increasing manner so that the severity of the initial onset is minimized. In the Lektra equipment this gradual increase is AUTOMATICALLY controlled for uniformity and consistency of results. The Glissando rate of rise, variable from .4 second to 2.0 seconds in steps of 0.2 second may be selected to regulate the degree of "glide" into the actual shock treatment. The Glissando is incorporated within the unit in such a manner that either Glissando Shock Therapy or Conventional Shock Therapy can be given at will.

Write Dept. N for Free Literature

LEKTRA LABORATORIES, inc.
154 ELEVENTH AVENUE—NEW YORK 11, N. Y.

Neurology

Role of the Brainstem in Blood Pressure Regulation in the Dog

J. D. McQueen, M.D., Kenneth M. Browne, M.D. and A. Earl Walker, M.D.

THIS study is part of a more comprehensive investigation of the role of the central nervous system in the genesis and maintenance of arterial hypertension. It was designed to determine the anatomy and physiology of those ganglionic masses and descending tracts in the brainstem concerned with cardiovascular functions in the dog. These brainstem structures consist mainly of the hypothalamus and the reticular nuclei of the pons and medulla, as well as their descending fiber tracts in the medial and lateral reticular substance of the brainstem. Although certain areas of the cerebral cortex are concerned with autonomic functions, a major portion of the vasomotor control exerted by the cerebral cortex appears to be mediated by non-myelinated fibers which descend in the pyramidal tracts.[1] However, these cortical influences may be more directly concerned with localized integrations of vasomotor and somatic activities than with the more fundamental function of regulating the systemic blood pressure. Probably it was these fibers passing through the internal capsule which were stimulated by Danilewski[2] and Sachs,[3] for Schüller[4] found that vasopressor responses were unobtainable after degeneration of the internal capsule.

Numerous studies, mostly in the cat, have demonstrated that the hypothalamus and brainstem are richly endowed with areas which yield marked

From the division of neurological surgery, The Johns Hopkins University School of Medicine, Baltimore.

This study aided by a grant from the Life Insurance Medical Research Fund.

vasomotor effects upon electrical excitation. In the detailed studies of Karplus and Kreidl,[5] Van Bogaert,[6] de Jaegher and Van Bogaert,[7] Hess,[8,9] and Kabat, Magoun, and Ranson,[10] the anatomic sites of vasomotor responses in the hypothalamus have been plotted precisely. In general, vasopressor responses were found by Hess[9] to be most common in the lateral and posterior hypothalamic regions, whereas vasodepressor points were more commonly encountered anteriorly and medially in the hypothalamus. However, there is considerable overlapping of the areas giving these opposing responses even in the hypothalamus.

The spatial distribution of vasomotor pathways in the brainstem reticular substance cannot be determined solely by stimulation technics because of the close anatomic relationship of descending tracts to reticular ganglionic masses which may constitute an "internuncial" vasomotor regulatory system. However, Magoun and Rhines[11] have demonstrated by stimulation that the brainstem reticular substance has a cephalic and medial inhibitory region and a lateral facilitatory area. This generalization confirms the observations of Wang and Ranson[12] who found that the lateral reticular substance of the entire rhombencephalon in the cat yielded vasopressor responses which were of the greatest magnitude when elicited from the caudal half of the medulla oblongata, whereas vasodepressor responses were characteristically obtained from points in the brainstem near the midline. When Thompson and Bach[13] demonstrated that lesions in the lateral reticular substance of the medulla diminished the vasopressor effect of a higher brainstem stimulation, whereas medially placed lesions of the medulla enhanced their effect, the above studies received further confirmation. These considerations suggested that lesions so placed in the brainstem as to interrupt predominately facilitatory pathways, while leaving intact a majority of the inhibitory ones, might influence favorably the neurogenic type of hypertension induced by sectioning the moderator nerves.

METHODS

A total of 43 experiments were carried out on adult dogs under local anesthesia. Intocostrin, 0.45 mg. per kg. of body weight, was given to immobilize the animal, and a Marshall respirator was used to aerate the dog artificially. Continuous blood pressure, pulse pressure, and pulse rate recordings were obtained from the femoral or aortic arteries using a Sanborn electromanometer.

The brainstem was explored and mapped by inserting a concentric needle electrode with a stereotaxic instrument. By means of dual electrodes in this needle the brainstem was stimulated with a thyratron discharge, the frequency of which was variable between 10 and 240 cycles per second and the voltage between 1 and 10 volts. Usually stimuli of frequencies of 30, 60, and 90 cycles per second and 3 volts were employed for a duration of 10 seconds.

In 14 experiments, electrograms were made from the brainstem and/or the cerebral cortex with a Grass electroencephalograph. The effects of tetraethylammonium chloride and the methonium drugs upon the vasomotor responses

elicited by excitation of various sites within the brainstem were determined in eight experiments. Finally, the effects of multiple needle tracts and electrocauterization in the hypothalamus and brainstem upon chronic neurogenic hypertension, due to moderator nerve section or occurring spontaneously in dogs under curare and local anesthesia, were determined. Lesions were verified by gross and microscopic examinations of serial sections of the brain stained for cells by Nissl's technic and for myelin by the Smith-Quigley method.

RESULTS

Localization of Vasomotor Effector Regions

Pressor areas. Pressor responses were evoked from stimulation of an area extending orally in the hypothalamus to the level of the optic chiasm and caudally in the medulla to the region of Deiters' nucleus. In the hypothalamus and subthalamus they were elicited from the following sites: the perifornical nucleus, the dorsal hypothalamic area, the posterior hypothalamic nucleus, and the zona incerta. In the midbrain, pressor responses were obtained from all portions of the central gray matter, the nuclei of the posterior commissure, at the superior border of the red nucleus, in the medial reticular formation, and in the region of the ventral nuclei of the brachium conjunctivum. In the medulla oblongata and pons they were induced from the medial and lateral reticular formations (figures 1 and 2). Pressor effects were not obtained from the cornu ammonis, pontine nuclei, or pyramidal tract. They occurred only in two of hundreds of thalamic stimulations.

Depressor areas. Depressor responses were infrequently obtained and never of as great amplitude as the pressor responses. Upon repetitive stimulation of a point giving a depressor response on the first stimulus, the response could rarely be reproduced and, if present, usually was of lesser degree than the primary one. Although occasionally a depressor response was obtained from the same point as a pressor using a lesser strength of stimulus, usually the two responses were obtained from areas separated by 1 or 2 mm. Depressor responses were evoked from the medial preoptic area, the lateral hypothalamic area, and in the region of the nucleus of the transverse peduncular tract.

Characteristics of the Responses

Types of response. Polyphasic responses were common (figure 3). A small depressor wave usually followed a specific pressor response and occasionally a second smaller pressor wave was then observed. These depressions occurred in areas from which no primary depressor activity could be demonstrated. Pressor responses of 150 mm. Hg were not uncommonly seen; the average response was approximately 40 mm. Hg. Responses obtained in 23 animals having an arterial hypertension of unknown etiology or induced by the bilateral resection of the carotid sinuses and transection of the vagal depressor fibers did not differ quantitatively or qualitatively from those elicited in normoten-

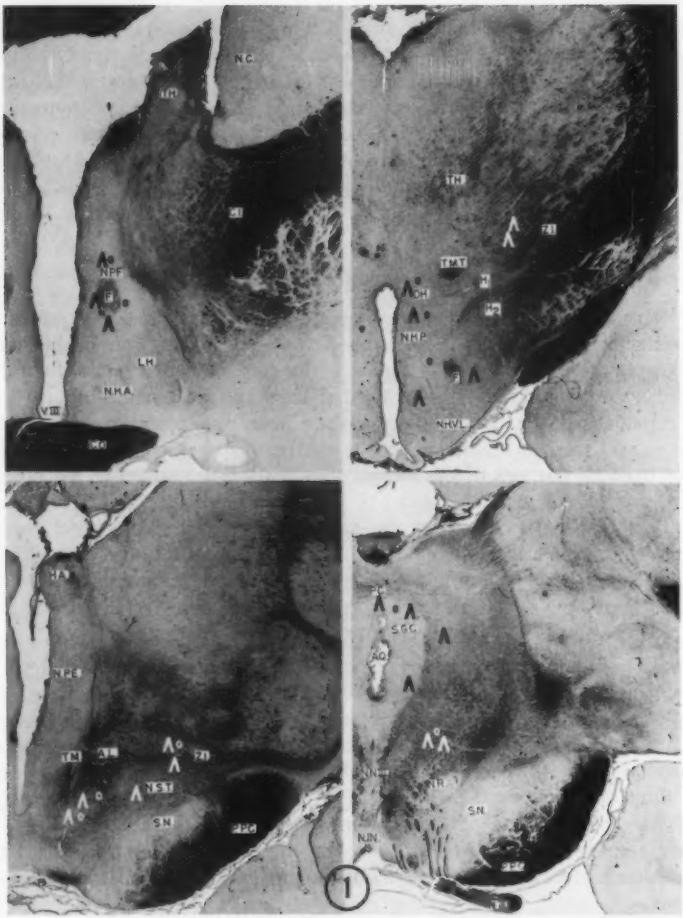


FIG. 1. Photomicrographs of representative sections of the brainstem of the dog with the points indicated at which vasomotor responses were obtained. The inverted "v"s indicate points at which pressor responses were obtained; the smaller circles indicate marked cardiac slowing associated with the rise in blood pressure.

Abbreviations: A.L.—ansa lenticularis; AQ.—aqueduct of Sylvius; B.C.—brachium conjunctivum; C.I.—internal capsule; C.O.—optic commissure; C.T.—trapezoid body; D.H.—dorsal hypothalamic area; F.—fornix; F.R.L.—lateral reticular formation; F.R.M.—medial reticular formation; H_1—field H_1 of Forel; H_2—field H_2 of Forel; HA.—habenula; L.H.—lateral hypothalamic area; L.M.—medial lemmiscus; N. III—oculomotor nerve; N. VII—facial nerve; N.C.—caudate nucleus; N.C.T.—central tegmental nucleus; N.D.—Deiters' nucleus; N.H.A.—anterior hypothalamic nucleus; N.H.P.—posterior hypothalamic nucleus; N.H.V.L.—ventrolateral hypothalamic nucleus; N. IN.—interpeduncular nucleus; N.M. V—motor nucleus trigeminal nerve; N.N. III—oculomotor nucleus; N.N. IV—trochlear nucleus; N. PE.—periventricular system; N.P.F.—perifornical nucleus; N.P.O.M.—parolivary nucleus; N.R.—red nucleus; N.S.T.—subthalamic nucleus; N.V.B.C.—ventral nucleus of the brachium conjunctivum; P.—pyramidal tract; P.C.—posterior commissure; P.P.C.—cerebral peduncle; S.G.C.—central gray matter; S.N.—substantia nigra; TH.—thalamus; T.M.—tract of Meynert; T.M.T.—mammillo-thalamic tract; V. III—third ventricle; V. IV—fourth ventricle; Z.I.—zona incerta.

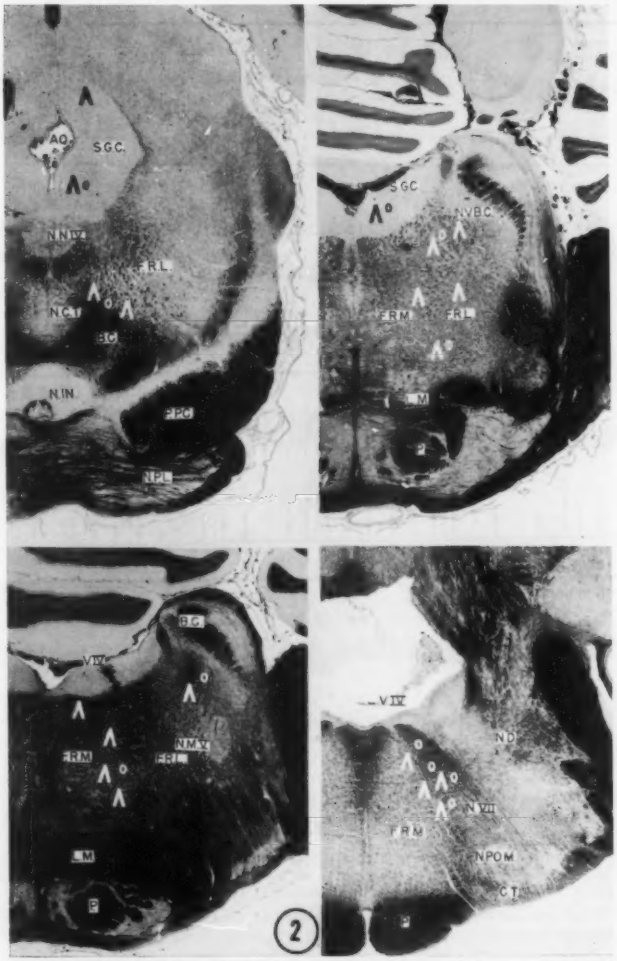


FIG. 2. Photomicrographs of lower brainstem — continuation of figure 1. (Symbols and abbreviations as in figure 1).

sive animals (figures 4 and 5). At hypotensive levels as low as 40 mm. Hg obtained by decreasing the blood volume, pressor effects still could be obtained.

Effect of frequency and intensity of stimulation. Both pressor and depressor effects were enhanced by increments of stimulus strength and frequency. The threshold for both responses was 2 to 3 volts, with the frequency of stimulation at 30 cycles per second. Since pressor and depressor points

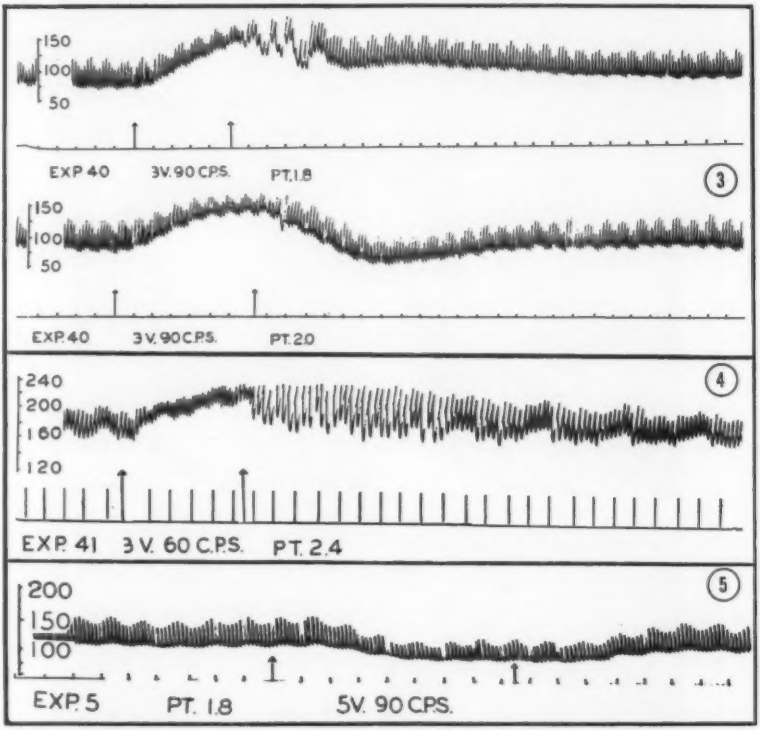


FIG. 3. Blood pressure tracings to show typical responses to brainstem stimulation. In the upper tracing a bradycardia develops after stimulation; in the lower tracing a secondary depression is seen. The two types of responses were obtained from points only 2 mm. distant; the upper tracing from a point 2 mm. dorsal to the lower in the medial reticular substance of the pons. The time scale is at 2 second intervals; arrows indicate the beginning and end of stimulation.

FIG. 4. Blood pressure tracing to show the rise in pressure in an animal which had an idiopathic arterial hypertension of 190/165 at the time of stimulation of the posterior lateral hypothalamus. The response is of the same character as that obtained in animals with normal pressures.

FIG. 5. Blood pressure tracing to show the depression of arterial blood pressure upon stimulation of the posterior hypothalamus.

commonly were within 1 to 2 mm. of each other a markedly supraliminal stimulus could excite both points, in which event the pressor effect always dominated. In one experiment, the depressor effect could be augmented by increasing the frequency of the stimulus; when the electrode was moved 2 mm., an initial depressor response at low frequency was obtained but at high frequency the response was pressor.

Effect on pulse rate. Changes in heart rate were commonly associated with the pressure alterations. Tachycardia was common and occurred initially with

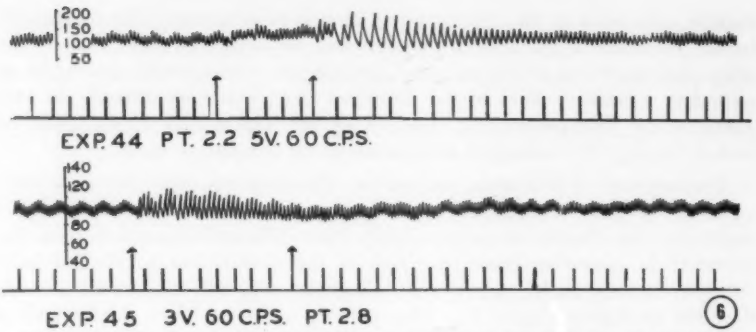


FIG. 6. Tracings to show the predominent effect of hypothalamic stimulation upon the heart rate.

the pressor response. Slowing of the heart rate with accompanying irregularities was much more common, and was usually a part of the total so-called pressor or depressor response (figure 6). They were occasionally found alone and those anatomical sites where they occurred predominately are indicated in figures 1 and 2 by circles.

Modification of Responses

The vasomotor effects were easily modified by a number of conditions. Pressor responses were abolished in 100 seconds by asphyxiation and returned in 120 seconds following an anoxic period of three minutes. The curarizing agent suppressed vasomotor responses minimally and usually transiently. However, it did potentiate the action of ganglionic blocking agents. Pentobarbital and ether in anesthetic doses completely abolished the vasomotor responses. The former agent was particularly potent in this respect. In a curarized animal having a spontaneously elevated blood pressure the hypertension could be reduced to normal and spontaneous pressure waves abolished with subanesthetic doses of pentobarbital, 1.0 to 2.5 mg. per kg.

The effects of methonium compounds and tetraethylammonium chloride upon experimental hypertensive states were studied. Pentamethonium bromide, hexamethonium chloride (but not the decane compound), as well as tetraethylammonium chloride were able to suppress both pressor and depressor responses (figure 7). The depressor effects and cardiac abnormalities were more easily abolished than the pressor effects. This abolition of pressor and depressor responses occurred even when the arterial pressure was only

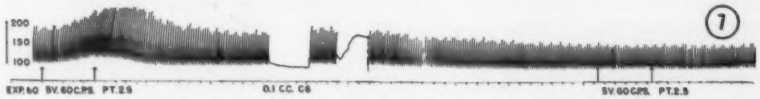


FIG. 7. Tracings to show abolition of the pressor responses obtained on hypothalamic stimulation by hexamethonium chloride. Note the slight decrease in blood pressure and pulse pressure.

slightly subnormal so that hypotension cannot be considered the responsible factor. However, if the arterial pressure was not depressed somewhat by the drug, the vasomotor responses were not altered. Occasionally an initial or secondary refractory state to the depressor drug was encountered. In rare instances the unresponsiveness induced by the hypotensive drugs could be broken through by prolonged stimulation of 30 seconds or more.

Electrograms of brainstem and cortex. Electrograms made from the electrodes at the point of stimulation usually were the same before and after the excitation. An afterdischarge was rarely seen. Electrocorticograms from the convexity in somewhat more than half of the stimulations so studied indicated an increase in frequency and voltage for a period of 1 to 20 seconds after the excitation (figure 8). This pattern was seen more clearly with a polyphasic pressor response. The "activation" lasted longer than the blood pressure elevation. At times pressor responses could be predicted by its presence; but it was not specific in that pressor effects were noted in its absence. Similarly, "activation" patterns were noted in the absence of blood pressure changes. These electrocorticographic changes were found upon stimulation of the lateral reticular formation in the medulla oblongata, the central gray matter of the midbrain, and the lateral hypothalamus.

Effect of Multiple Lesions in the Brainstem

Dogs operated upon under local anesthesia and artificially aerated after the administration of curare often had an elevated systolic and diastolic blood pressure which was frequently, but not always, associated with an accelerated heart rate. This hypertension could be abolished with light anesthesia, especially by pentobarbital sodium. Despite numerous needle tracts and repeated small electrocautery lesions at pressor points, these dogs usually remained hypertensive throughout the experiment. A typical example was dog H8. This dog was immobilized with d-tubocurarine, artificially aerated, and a suboccipital craniotomy was performed under local anesthesia. A continuous blood pressure recording then was begun, and the initial reading was 200/100 with a pulse of 84. A total of 64 stimulations at 49 points along four needle tracts were carried out during the four-hour period of the experiment. Four cauterizations of vasopressor points, each of which effectively abolished the vasopressor response at that particular site, were carried out. Despite a bradycardia of 54, the blood pressure was 200/90 at the end of the experiment.

Three dogs with chronic neurogenic hypertension were subjected to similar acute experiments, at which time multiple needle tracts were made in the course of the mapping out of vasomotor responses. All of the dogs remained hypertensive at the end of the experiments despite electrocautery lesions of multiple vasopressor sites.

In a series of eight acute experiments upon normal dogs and dogs with an acute hypertension induced by section of the moderator nerves and excision of the carotid sinuses, it was demonstrated that the vasopressor response of a given site within the brainstem could be abolished or even reversed by mul-

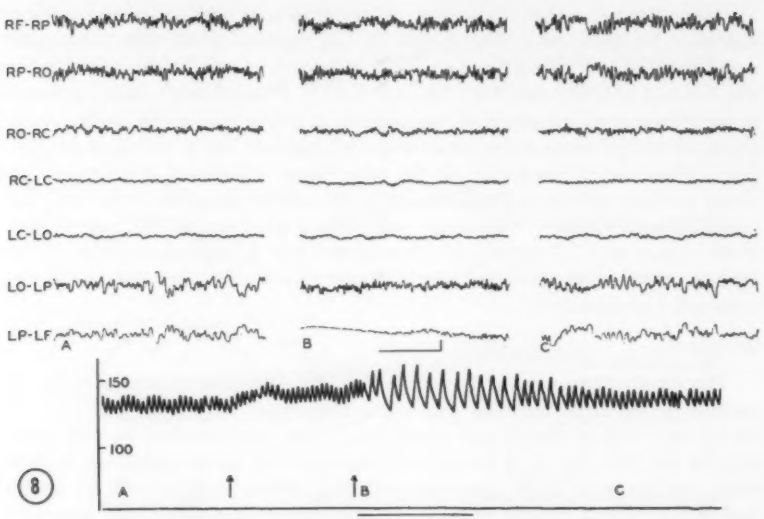


FIG. 8. Electrocorticograms and blood pressure tracing to show the "activating" effect of stimulation during the rise in blood pressure. The electrocorticograms (A, B, and C) were taken at approximately the times indicated by the letters A, B, and C on the blood pressure tracing below. The increased frequency of cortical waves in the parietal and frontal regions is apparent.

The horizontal line at the base of the electrocorticogram tracings represents an interval of 1 second; the vertical line a calibration of 100 uv. The horizontal line at the base of the blood pressure record indicates an interval of 10 seconds.

Abbreviations: LC—left cerebellar needle electrodes; LF—left frontal needle electrodes; LO—left occipital needle electrodes; LP—left parietal needle electrodes; RC—right cerebellar needle electrodes; RF—right frontal needle electrodes; RO—right occipital needle electrodes; RP—right parietal needle electrodes.

tiple, large lesions in the brainstem, but such lesions did not necessarily block the vasopressor response elicited from another site within the brainstem. Dog R6 may be cited as an example of this series of experiments. This normal stock dog was curarized, then aerated artificially. An electrode holder was screwed in place on the calvarium at the vertex and five burr holes were made just to the right of the midline to allow the introduction of number 20 gauge, concentric needle stimulating electrodes. The five electrodes then were inserted into the hypothalamus and mesencephalon until good vasopressor responses were obtained with stimulation between adjoining electrodes. An x-ray film of the skull was taken at this stage to check the position of the electrode tips (figure 9). Stimulation of the hypothalamus in the region of the right supramammillary nucleus (figure 9, E, electrodes 1-3) elicited an excellent vasopressor response (figure 9, A-A[1]). Bilateral incisions of the lateral reticular substance at the level of the eighth nerve on the left and slightly caudal to that level on the right side failed to diminish the vasopressor effect of the supramammillary stimulation. The heart rate increased to 198 per min-

ute from 108 per minute, however. Bilateral incisions of the lateral reticular substance at the level of the inferior olivary nucleus resulted in the appearance of an initial vasodepressor response but the secondary blood pressure rise reached 215/155 mm. Hg (figure 9 C-C^1). Finally, large bilateral lesions in the dorsolateral quadrant of the medulla at the caudal extent of the decussation of the pyramids were associated with marked fall in the diastolic pressure subsequent to excitation of the same point stimulated previously. The blood pressure fell from 195/130 to 170/80 and the secondary rise was minimal (figure 9, D-D^1). However, when the next most caudal pair of electrodes (electrodes 5-7, figure 9 E), were stimulated, a vasopressor response was again elicited despite the multiple brainstem incisions. Moreover, the animal remained hypertensive.

DISCUSSION

The localization of areas giving pressor and depressor responses along the midline of the hypothalamus and lower brainstem, well established for the cat by the work of Kabat and coworkers,[10] and demonstrated by this investigation for the dog, is of particular interest in the consideration of homeostatic mechanisms. In the same general area of the cerebral axis are ganglionic masses which regulate other sympathetic and parasympathetic functions, such as water metabolism, piloerection, sudomotor regulation, and so on. The intimate association of these vegetative centers presumably allows for an easy integration and coordination of the general homeostasis of the organism since Chen and co-workers,[14] and Lim and co-workers[15] have noted that several sympathetic responses may be obtained by stimulation of one point. This is in contradistinction to the autonomic centers of the cerebral cortex on the convexity of the hemispheres which, as Fulton[16] has emphasized, are concerned more specifically with the functioning of the somatic aspects of the organism's existence. Thus, as movements are initiated, appropriate vasomotor adjustments are made. It is not surprising then that the pathways mediating these cortical sympathetic impulses do not pass through the hypothalamus whereas, as Wall and Davis[1] showed, those from the orbitotemporal cortex do.

The general characteristics of the pressor and depressor responses, so well described by Kabat and co-workers[10] and Hess[9] for the cat, are much the same in the dog. In accord with the former group but not with the latter, we have had difficulty demonstrating depressor effects. Perhaps this is due to the form of stimulus used, since Hess emphasized the necessity of using a square wave stimulus of low frequency. Although we have used routinely low frequency stimulation, we were never able to demonstrate to our satisfaction that a change in frequency altered the response, other than might be obtained by the increased energy given by the higher frequency stimulus. This is not in agreement with the findings of Bronk and co-workers[17] and Hare and Geohagen[18] who have suggested that depressor responses were enhanced by a stimulus of low frequency. This interesting aspect of the problem requires further study.

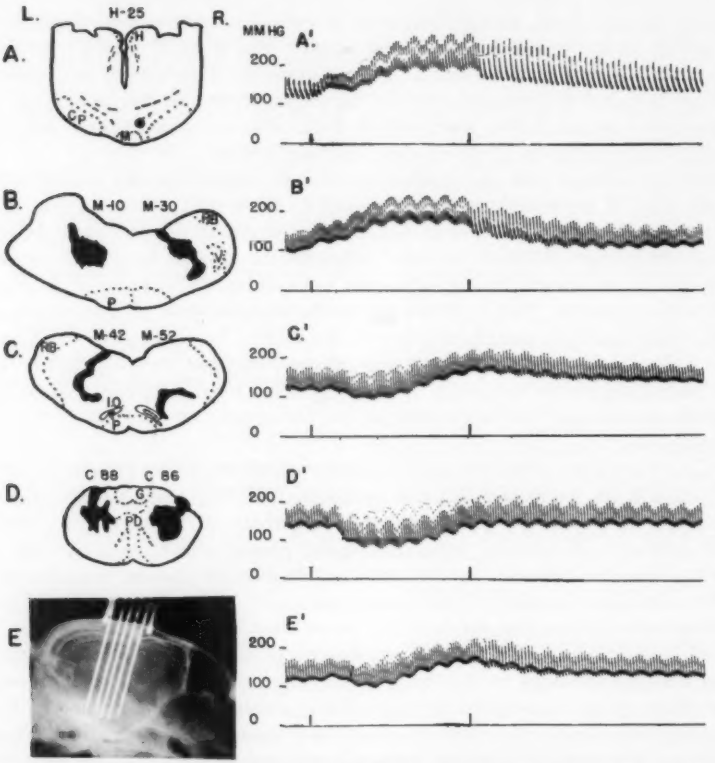


FIG. 9. A moderate hypertension (160/110) developed in this animal after immobilization with Intocostrin and intubation for artificial respiration. Five concentric needle electrodes were inserted into the region of the right hypothalamus and mesencephalon under roentgenographic control (*E*). At the end of the experiment a cautery current was applied to each electrode for subsequent histologic determination of its exact situation. Electrodes from right to left (anterior-posterior) are numbered 1, 3, 5, 7, and 9.

A–A¹. Stimulation (16 secs. 90c/s and 2 v.) of the supramammillary region through electrodes 1 and 3 (*E*) resulted in a marked vasopressor effect which reached 280/200 mm. Hg. The period of the stimulation is indicated on the base line of each blood pressure record, which was obtained from the femoral artery with an electromanometer.

B–B¹. The above vasopressor effect was little altered by bilateral lesions of the lateral reticular susbtance at the level of the eighth nerve on the left and slightly caudal to that level on the right side.

C–C¹. Stimulation subsequent to bilateral lesions in the lateral reticular substance at the level of the inferior olivary nucleus resulted in an initial vasodepressor effect for only 6 seconds followed by a secondary rise to 215/155 mm. Hg at the end of the stimulation.

D–D¹. Stimulation subsequent to large bilateral lesions of the dorsolateral quadrants of the medulla at the caudal extent of the decussation of the pyramids was followed by a marked fall in the diastolic pressure from 130 mg. Hg and the secondary rise in blood pressure was minimal. (Compare with A–A¹).

E–E¹. Stimulation between electrodes 5 and 7 resulted in a marked vasopressor effect despite the six brainstem lesions which effectively blocked the vasopressor effect of the more anterior stimulation (electrodes 1 and 3). The dog's blood pressure remained elevated at 180/125 at this stage.

The latency, form, and prolongation of pressor responses have been well described by Karplus and Kreidl[5] and later by Van Bogaert[6] and de Jaegher and Van Bogaert.[7,19] The cardiac slowing noted by Danilewski[2] and shown by Van Bogaert[6] to be transmitted by the vagus nerve and not influenced by buffer nerve section is also prominent in dogs. This response seems to be particularly susceptible to the ganglionic blocking agents.

It is of interest that the central vasomotor mechanisms are not affected by the state of the peripheral vascular system. Even with an arterial pressure of 200 mm. Hg, the responses to brainstem stimulation are the same as obtained with a normal blood pressure. Although the afferent vasomotor regulatory systems are intact, they do not seem to modulate the activity of the central pressor centers. This is of interest in the consideration of hyperpiesia in man, for if the same principles apply in the human being as in the dog, any factor chronically elevating the arterial pressure may not be compensated by the central vasomotor regulation. But on the other hand, all stresses upon the central mechanisms will cause rises in the blood pressure as if it were at a normal level.

That the effects of brainstem stimulation are abolished by ganglion blocking drugs is an interesting but not unexpected finding, since vasomotor impulses are mediated over the peripheral sympathetic nervous system. Rarely will prolonged stimulation induce a delayed pressor effect. Whether this is due to adrenalin secretion as Houssay and Molinelli[20] showed might occur, or to a hormonal-neurogenic vasopressor substance as hypothecated by Taylor and co-workers[21] is unknown.

It has been suggested that the persistence of vascular response to brainstem stimulation might be due to afterdischarge of the stimulated neurones. The electrograms made from the stimulating electrodes seem to negate this possibility for rarely was an afterdischarge seen associated with a rise in blood pressure. The cortical "alerting" response seen occasionally suggests that the vasomotor centers are in close proximity to association areas of the diffuse reticular system. Although this is not a constant association it probably does indicate a certain integration of the peripheral autonomic effect and the central "alerting" response of the reticular system.

SUMMARY

1. Pressor and depressor points of the brainstem of the dog are mapped. In general they are located in areas comparable to those of the cat.

2. The vasomotor changes are abolished by sympathetic blocking agents such as the methonium drugs; the pressor responses are more resistant to the action of such drugs than the depressor and cardiac responses.

3. The level of the blood pressure, within limits, does not alter the quantitative or qualitative responses to brainstem stimulation.

4. The significance of these findings for the homeostasis of the animal is discussed.

REFERENCES

1. Wall, P. D., and Davis, G. D.: Three cerebral cortical systems affecting autonomic function, J. Neurophysiol. 14:507, 1951.
2. Danilewski, B.: Experimentelle Beitrage zur Physiologie des Gehirns, Arch. ges. Physiol. 11:128, 1875.
3. Sachs, E.: On the relation of the optic thalamus to respiration, circulation, temperature and the spleen, J. Exper. Med. 14:408, 1911.
4. Schüller, A.: Reizversuche am Nucleus caudatus des Hundes, Arch. ges. Physiol. 91:477, 1902.
5. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: IV. Mitteilung, Arch. ges. Physiol. 171:192, 1918.
6. Van Bogaert, A.: Régulation hypothalamo-hypophysaire de l'appareil circulatoire, Arch. mal. coeur 29:109, 1936.
7. de Jaegher, M., and Van Bogaert, A.: Hypertension hypothalamique expérimentale: Sa nature, Compt. rend. Soc. biol. 118:546, 1935.
8. Hess, W. R.: Das Zwischenhirn und die Regulation von Kreislauf und Atmung, Leipzig, G. Thieme, 1938.
9. Hess, W. R.: Das Zwischenhirn: Syndrome, Lokalisationen, Funktionen, Basel, Benno Schwabe & Co., 1949.
10. Kabat, H., Magoun, H. W., and Ranson, S. W.: Electrical stimulation of points in the forebrain and midbrain: The resultant alterations in blood pressure, Arch. Neurol. & Psychiat. 34:931, 1935.
11. Magoun, H. W., and Rhines, R.: An inhibitory mechanism in the bulbar reticular formation, J. Neurophysiol. 9:165, 1946.
12. Wang, S. C., and Ranson, S. W.: Autonomic responses to electrical stimulation of the lower brainstem, J. Comp. Neurol. 71:437, 1939.
13. Thompson, W. C., and Bach, L. M. N.: Some functional connections between hypothalamus and medulla, J. Neurophysiol. 13: 455, 1950.
14. Chen, M. P., Lim, R. K. S., Wang, S. C., and Yi, C. L.: On the question of a myelencephalic sympathetic centre: III. Experimental localization of the centre, Chinese J. Physiol. 11:367, 1937.
15. Lim, R. K. S., Wang, S. C., and Yi, C. L.: On the question of a myelencephalic sympathetic centre: VII. The depressor area a sympathoinhibitory centre, Chinese J. Physiol. 13: 61, 1938.
16. Fulton, J. F.: Functional localization in the frontal lobes and cerebellum, London, Oxford University Press, 1949.
17. Bronk, D. W., Pitts, R. F., and Larrabee, M. G.: The role of the hypothalamus in cardiovascular regulation, A. Research Nerv. & Ment. Dis., Proc. 20:323, 1940.
18. Hare, K., and Geohegen, W. A.: Influence of frequency of stimulus upon response to hypothalamic stimulation, J. Neurophysiol. 4:266, 1941.
19. de Jaegher, M., and Van Bogaert, A.: Régulation de la tension artérielle et hypothalamus, Compt. rend. Soc. biol. 118:544, 1935.
20. Houssay, B. A., and Molinelli, E. A.: Centre adrénalino-sécréteur hypothalamique, Compt. rend. Soc. biol. 93:1454, 1925.
21. Taylor, R. D., Page, I. H., and Corcoran, A. C.: A hormonal neurogenic vasopressor mechanism, Arch. Int. Med. 88:1, 1951.

The commonest form is the so-called "epigastric aura," a sensation referred to the pit of the stomach, present in one-half (51 cases). In a third of these it was actual pain; in half it was a vague indescribable sensation; in the remainder it was described as a feeling of "burning," of "coldness," of "trembling," of "something there," or of "winding up." In most cases it was referred to the epigastric region generally; in a few it was a little to the left; in none to the right. In two it commenced lower in the abdomen; in several it was referred to both the epigastrium and the lower part of the sternum. Whenever the sensation was actual pain, it remained at the epigastrium until consciousness was lost. In many of the cases in which the sensation was vague, it was described as "rising up through the chest" to the throat of head. The passage to the head was usually followed by immediate loss of consciousness; that to the throat by a sensation of choking. This latter reminds us of the well-known sensation in hysteria, and in many cases of genuine epilepsy the sensation appears to be exactly the same as the globus hystericus.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Some Innovations in Human Stereoencephalotomy

José M. R. Delgado, M.D.,
Hannibal Hamlin, M.D. and Donald Jay Nalebuff, D.M.D.

STEREOENCEPHALOTOMY has been used as an aid in human brain surgery procedures since 1947 when Spiegel and Wycis and their co-workers modified methods previously restricted to the experimental animal.[1] More recently, stereotaxic instruments have been devised by Bailey and Stein,[2] Hayne and Meyers,[3]Hodes and co-workers,[4] Jasper and Hunter,[5] Leksell,[6] Pertuiset,[7] the Spiegel group,[1,8,9] Sweet,[10] Monnier,[11] and Talairach and co-workers,[12] all of which are designed to improve upon the original modification.

It is the purpose of this paper to describe methods of stereoencephalotomy which may obviate certain difficulties. The following innovations are introduced: 1) use of an optical rather than a mechanical technic for alignment to the standard reference planes; 2) utilization of the teeth and their supporting structures as a means of rigid fixation of the instrument; 3) modification of standard cephalometric roentgenographic procedures to show comparative localization of multilead electrodes placed within the brain and to contribute anthropometric information on craniocerebral relationship; and 4) intracerebral implantation of multilead electrodes for electroencephalographic recording, electrical stimulation, and therapeutic focal electrocoagulation.

MATERIALS AND METHODS

The construction and utilization of multilead electrodes for long term implantation has been described elsewhere.[13] Study of the electrical activity of the brain in the conscious patient for a period of several days, involving the effects evoked by electrical stimulation, has been used by us to direct the placement of electrolytic lesions as a therapeutic measure.[14,15] It was suggested at that time that implantation of these electrodes was to be accomplished with a new stereotaxic instrument, which has now reached a stage of development that merits description.

From the Yale Aeromedical Research Unit, departments of physiology and psychiatry, Yale University School of Medicine, New Haven, Connecticut, and the State Hospital for Mental Diseases, Howard, Rhode Island. This investigation was supported in part by a research grant from the Foundations' Fund for Research in Psychiatry.

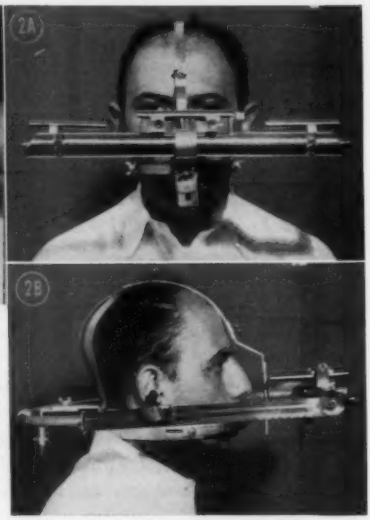


FIG. 1. Taking advantage of a natural stable element, the maxillary teeth or the alveolar ridge in edentulous patients, a plastic bite block is used as rigid support for a substructure attached to the stereotaxic instrument.

FIG. 2A and B. Frontal and lateral view of a human subject with the stereotaxic apparatus in position. With the optical sighting system, the instrument is adjusted to symmetrical points of the inferior orbital arch and to both external auditory meati (Ried's base line).

The instrument is composed of a mask-like framework, the substructure, to which is attached an intraoral bite block (figure 1), and an adjustable superstructure which carries the brain electrodes as well as an optical system for orientation along the standard reference planes (figure 2). Immobility of the entire instrument is achieved by means of a transparent plastic bite block at the end of a rigid rod, constructed on a plaster cast of the patient's dentition. The bite block fits into place tightly between the subject's upper and lower teeth, the free end of the rod extending from the mouth. The rod is then joined to the anterior framework of the substructure. In edentulous individuals fixation may be achieved by using the upper alveolar ridge itself as the firm element. The required adjustments are made on each side until stability is obtained, that is, when the subject's head and neck and the stereotaxic framework move as one. The superstructure is slipped over the basic framework and attached both anteriorly and posteriorly. Adjustments to the proper orientation planes are accomplished by optical sighting devices, and parallelism is achieved by alignment to points marked along Ried's base line. The instrument is comfortable to hold and tolerated easily without anesthesia.

Preoperative x-ray films are taken by seating the subject in a levitation chair, with the substructure of the instrument and its intraoral bite block properly attached. The Ried's base line of the subject is adjusted to be parallel to the floor and perpendicular to the x-ray plate. Once this position is achieved, it is maintained by locking the superstructure to a clamping device for a few moments. A central x-ray beam passes through both external auditory meati and thus strikes the center of a laterally-placed film cassette. An

anteroposterior film is then taken by rotating the chair 90° toward the x-ray tube, which allows the central ray to pass through the midsagittal plane of the head at the level of a line connecting the inferior orbital margins of both sides. In either case the x-ray beam, the film cassette, and the position of the subject's head maintain a constant relationship. This cephalometric technic is derived from methods currently used in orthodontic evaluation studies.[16–19]

Preplacement calculations of the desired electrode positions are dependent on the determination of fairly constant reference points within the brain and an exact knowledge of the location of the area to be electrocoagulated in relation to these reference points. Certain points are available and have been used in stereoencephalotomy procedures. The calcified pineal body, if observable radiologically, may serve as such; if not, pneumoencephalography may be performed and other landmarks such as the posterior commissure utilized.[9] This technic should make it possible to obtain anthropometric data concerning the relationship between reference points within the brain and cardinal bony points of the skull.

The desired position relative to a chosen intracerebral reference point is calculated along tridimensional coordinates. Variations in brain size and shape are noted and taken into account when making the necessary calculations. Once the site has been determined, the operation to implant electrodes is performed. In cooperative patients local anesthesia is sufficient since the operation is usually brief; if not, general anesthesia may be employed. The multilead electrodes are introduced at predetermined sites through 15 mm. burr holes. An electrode is fixed in position at its exit by adapting its lead to the wall of the burr hole and by suture attachment to the scalp.

After operation, x-ray films are taken in the same way as described above to enable the neurosurgeon to check the accuracy of electrode placement. Usually four needle electrodes are used. As each electrode is formed by seven separate leads, 28 different points within the brain may be studied and eventually coagulated in each patient. The electroencephalographic and neurophysiologic study of each point provides a functional check of the position of each lead, which is a great advantage since anatomic and physiologic variations within the brain are unpredictable even with the most perfect stereotaxic technic. Electrocoagulation of each point is performed in the fully conscious patient and is not painful. In this way, the effects of fiber tract interruption may be observed step by step. This is especially helpful in cases of intractable pain. Coagulation of other points may be continued or discontinued over a period of several days depending on the therapeutic response. When the procedure is regarded as complete the electrodes are withdrawn, a process which patients have also tolerated without anesthesia.

DISCUSSION

The original Horsley-Clarke stereotaxic instruments[20] were constructed to attach to the head of the animal along standard reference planes, the midsagittal, the interaural, and a plane extending from the external auditory

meatus of one side to the inferior orbital margin of the same side, and these lines of reference have been maintained in the design of newer instruments. The Horsley-Clarke instrument, however, employed fixation mechanisms which are unsuitable for human stereoencephalotomy since they are not only quite painful without anesthesia but may lead to tissue damage as well. Other means of stabilization have been sought in the past. Two types of fixation are currently utilized which may be designated as the rigid and the nonrigid.

Examples of the latter type are the instruments developed by Spiegel and his associates during the past six years. The original "stereostat" consisted of a ring base fixed to the scalp by means of a plaster head cap. This was found to be unmanageable in some patients, time-consuming, and impractical because of the difficulty encountered in aligning the apparatus parallel with Ried's base line.[1] Newer models were made to carry two ear plugs and two orbital bars which would insure proper alignment when in position. The instrument was designed to be removed during roentgenography, and a means of insuring accurate replacement had to be incorporated. Therefore, tattoo marks were made in the scalp of the subject at the original points of contact of five or more vertically placed adjustable pins so that the points could be reseated upon their respective tattoo marks.[8] These methods have the disadvantage of relying on the freely movable scalp as the basic foundation for stability of the instrument.

The alternate method of rigid fixation has been employed by Hayne and Meyers,[3] Sweet,[10] and Talairach and co-workers.[12] Here the instrument is secured by introducing paired opposite pegs through anesthetized spots of scalp which are then tapped into the outer table of the calvarium. It is felt that equally secure stability can be obtained more readily by taking advantage of the maxillary bone and upper teeth. The fixation is rigid, yet removable at will, and is comfortable for the patient; no anesthesia is required and the operator can reseat the instrument with confidence that it has been returned precisely to its previous position. Construction of the inexpensive plastic bite block for each patient should be obtained several days before the operation. It is also possible to attach the substructure to a dental tray filled with impression compound, so that maxillary fixation of the instrument may be accomplished in a few minutes.

The value of x-ray studies taken after the electrodes have been implanted in their calculated sites is self-evident. This technic aims to place the head of the subject in a standard position so that distortion of x-ray films from a standard source will be uniform; therefore, calculation of the position of intracranial electrodes is facilitated and comparative craniocerebral measurements made possible.

SUMMARY

It has been the purpose of this paper to describe a new technic of stereotaxic instrumentation to be used for certain operative procedures on the human brain. The following innovations have been introduced:

1. The use of an optical method of obtaining the standard orientation of a new stereotaxic instrument.

2. The use of an intraoral appliance fixed to the teeth whose supporting structures serve as a means of rigid stabilization during intracerebral electrode placement.

3. Cephalometric x-ray studies which enable verification of intracerebral electrode location by comparing post-electrode placement films with earlier reference films prior to producing therapeutic subcortical lesions, as well as accumulation of anthropometric data of craniocerebral relationship.

4. The implantation of multilead electrodes within the brain which allows the operator to record the electrical activity of focal areas and to stimulate and select points for therapeutic electrocoagulation.

The pilot model of the stereotaxic instrument was constructed at the Torres Quevedo Institute, Madrid, Spain. We wish to express our great appreciation to Professors Juan M. Torroja and Vicente Urbistondo for their generous help and advice. The substructure was constructed by John Marshall, superintendent of the Yale Aeromedical Research Unit, to whom we also express our appreciation.

REFERENCES

1. Spiegel, E. A., Wycis, H. T., Marks, M., and Lee, A. J.: Stereotaxic apparatus for operations on the human brain, Science 106:349, 1947.
2. Bailey, P., and Stein, S. N.: A stereotaxic apparatus for use on the human brain, A.M.A. scientific exhibit, Atlantic City, June 1951.
3. Hayne, R., and Meyers, R.: An improved model of a human stereotaxic instrument, J. Neurosurg. 7:463, 1950.
4. Hodes, R., Heath, R. G., Founds, W. L., Llewellyn, R. C., and Hendley, C. D.: Implantation of subcortical electrodes in man by stereotaxic technique, Am. Physiol. Soc. exhibit, New Orleans, September 1952.
5. Jasper, H., and Hunter, J.: A stereotaxic instrument for man, Am. EEG Soc. exhibit, Atlantic City, June 1949.
6. Leksell, L.: A stereotaxic apparatus for intracerebral surgery, Acta chir. scandinav. 99:229, 1949.
7. Pertuiset, B.: Présentation d'un appareil stéreotaxique adapté à l'homme, 14e Congrès, Soc. Internat. de Chir., Paris, September 1951.
8. Spiegel, E. A., Wycis, H. T., and Thur, C.: The stereoencephalotome. (Model 111 of our stereotaxic apparatus for operations on the human brain.) J. Neurosurg. 8:452, 1951.
9. Spiegel, E. A., and Wycis, H. T.: Stereoencephalotomy, New York, Grune & Stratton, 1952.
10. Sweet, W.: Personal communication, 1953.
11. Monnier, M.: Somatotopy of the thalamus in man (Results of electrical stimulation). XIX Intrntl. Physiol. Cong. Abstr. 628, 1953.
12. Talairach, J., Hecaen, H., David, M., Monnier, M., and Ajuriaguerra, J.: Recherches sur la coagulation therapeutique des structures souscorticales chez l'homme, Rev. neurol. 81:4, 1949.
13. Delgado, J. M. R.: Permanent implantation of multilead electrodes in the brain, Yale J. Biol. & Med. 25:351, 1952.
14. Delgado, J. M. R., Hamlin, H., and Chapman, W. P.: Technique of intracranial electrode implacement for recording and stimulation and its possible therapeutic value in psychotic patients, Confinia neurol. 12:315, 1952.
15. Grantham, E. G.: Prefrontal lobotomy for relief of pain: with a report of a new operative technique, J. Neurosurg. 8:405, 1951.
16. Broadbent, B. H.: A new x-ray technique and its application to orthodontia, Angle Orthodontist 1:45, 1931.
17. Margolis, H. I.: Standardized x-ray cephalographics, Am. J. Orthodontics 26:725, 1940.
18. Pacini, A. J.: Roentgen ray anthropometry of the skull, J. Radiol. 3:230, 322, and 418, 1922.
19. Wylie, W. L.: Cephalometric roentgenography and the dentist, Am. J. Orthodontics 31: 341, 1945.
20. Horsley, V., and Clarke, R. H.: The structure and functions of the cerebellum examined by a new method. Brain, 31:45, 1908.

Acquired Epilepsy
A Study of 535 Cases

Bushnell Smith, M.D., Geoffrey C. Robinson, M.D. and William G. Lennox, M.D.

ETIOLOGICALLY, persons having epileptic seizures are generally divided into two groups. The seizures of one group are based on a transmitted "constitution" or tendency to seizures, the other on some pathologic change in the brain acquired after conception. In some persons both factors contribute. This presentation will consider those patients whose history or examinations point to a structural change in the brain, gross or microscopic, that antedated the first seizure and hence might account wholly or in part for the epilepsy.

From the standpoints of prevention and treatment this subject is of much interest, yet suprisingly little has been reported on groups of non-institutional patients. Much depends on the selection of cases, whether children or adults, civilian or military, and whether a neurologist or a neurosurgeon is reporting. The completeness and interpretation of data also make a difference.

MATERIAL AND METHODS

The material presented here was drawn from a mixed group of 2,090 epileptic patients whose records were carefully reviewed. The data for 1,648 proved adequate. Of these 535, or 32.5 per cent, were believed to have evidence of a neuropathologic lesion that antedated the first seizure. Twenty-two per cent had a family history of epilepsy and 2.4 per cent a family history of both epilepsy and migraine. In a control group of hospital personnel numbering 722, only 6.6 per cent reported known epilepsy among relatives.[1]

Of the 535 patients, 69 per cent were persons of all ages, seen privately, and 31 per cent were children mostly under the age of 12, seen in the Seizure Clinic of the Children's Hospital. Ninety per cent had had seizures before the age of 20.

Regarding examinations, less than 15 per cent of the group had been studied as in-patients. However, the following evidence was utilized: a de-

From the Children's Medical Center, Boston.
This is No. LXII in a series, "Studies in Epilepsy."
Aid received from U. S. Public Health Service, Department of Health, Education and Welfare, and the Rockefeller Foundation.

tailed history of any event that pointed to some structural abnormality of the brain antedating the first seizure; localizing evidence from the aura, or from the description of the early seizure; abnormal neurologic signs; focal abnormalities of the electroencephalogram; distortion of the ventricular system on pneumoencephalography; or abnormalities of the spinal fluid. Some findings point to gross structural damage; others such as a transient hemiparesis or a focal seizure discharge may mean only temporary or minimal damage.

The examiner encounters two difficulties. First, when two or more causes are found, which is the principal one? The multiple causes of epilepsy in an individual patient have been emphasized.[2] In the present series, for example, 28 of the 161 persons noted as having had "birth complications" had possible injuries later. Of these persons 13 had had trauma, nine febrile convulsions, five cerebral infections, and one diabetes. Of the 41 born prematurely, five later had cerebral infections and three experienced head trauma. Second, how definite must the evidence of an acquired lesion be? On this point Bridge,[3] in analyzing a group of 742 patients 12 years of age or younger, observed some evidence of an acquired cause in 70 per cent, divided as follows: possible or probable 20 per cent, definite but minimal 19 per cent, definite and moderate 14 per cent, and pronounced 17 per cent. The interpretation of evidence is a matter of clinical experience and judgment.

DISTRIBUTION OF CAUSES IN VARIOUS GROUPS

Differences in selection of cases and in the author's interpretation of evidence produce wide differences in the assignment of cause. Table 1 compares distribution of causes in the 469 cases of the present series (after elimination of 66 cases in which assignment of cause was not made) with 458 patients collected by one of the authors prior to 1939. Patients of the earlier series were older than those in the present series, and 26 per cent had their first seizures

TABLE 1

ACQUIRED CAUSES OF EPILEPSY IN A PREVIOUS AND THE PRESENT SERIES

Acquired Causes	*Prior Series*		*Present Series*		*Both Series*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Paranatal	120	26.2	232	49.4	352	38.0
Postnatal trauma	122	26.6	111	23.8	233	25.2
Infections, including febrile	90	19.7	92	19.5	182	19.5
Brain tumor	54	11.8	9	1.9	63	6.7
Circulation	40	8.7	8	1.7	48	5.3
Other causes	32	7.0	17	3.7	49	5.3
Total	458	100.0	469	100.0	927	100.0

after age 20 as compared with only 10 per cent of those in the present series. This would explain the smaller representation of paranatal conditions and the larger proportion of cases of brain tumor and circulatory diseases in the earlier series.

In the 927 cases of both series to which some cause was assigned, the most frequent cause referred to some condition before, during, or immediately after birth, 38 per cent. Next was postnatal trauma, 25.2 per cent; infections, 19.5 per cent; brain tumor (not always confirmed by operation or autopsy), 6.7 per cent; and disorders of circulation, 5.3 per cent.

The data of Bridge deal with 371 children below the age of 12 having definite evidence of pathologic lesion (one-half of his total series).[3] The differences between his series and the present group seem too great to be accounted for by age or other selection of cases. Probably differences in diagnostic criteria were more important. "Vascular occlusions" accounted for 24.3 per cent of Bridge's cases, but "circulatory disorders" for only 1.7 per cent of ours; "encephalitis and syphilis" for 6.3 per cent of his, "infections" for 19.5 per cent of ours; postnatal head injuries for 14.6 per cent of his, and for 23.8 per cent of ours. Both series were in agreement about the importance of birth complications. "Congenital, birth, and neonatal injuries" were credited with causing 49.9 per cent of acquired epilepsy in Bridge's study at Baltimore, and these factors plus prematurity with 49.3 per cent in our study. Birth injury accounted for 14.2 per cent of Peterman's[4] total group of 2,500 epileptic children. If based on symptomatic (acquired) cases only, the proportion would probably approach that of the Baltimore and Boston studies.

These observations and those of Courville and Marsh,[5] Schreiber,[6] and other authors seem directly opposed by the report of Keith and co-workers.[7] They followed children whose birth was normal or abnormal for from one to seven years after birth. Prolonged labor doubled the death rate among 402 children, and in 236 others asphyxia multiplied the death rate more than five times. However, among children who survived, the authors "found no evidence that prolonged labor, asphyxia, or delayed respiration caused any neurologic abnormality." This applied to premature as well as full-term infants. In fact, in the first seven years after birth there were fewer convulsions (1.7 per cent) in the group in which there was prolonged labor and asphyxia than among the controls (2.8 per cent). However, epilepsy apparently based on birth injury may not appear until puberty or even later.

Among the total epileptics screened by Bridge, Peterman, ourselves, and Alström,[8] the proportion believed to have experienced pathologic brain changes in the paranatal period was respectively 25, 14, 14, and 6 per cent. The last group was composed mostly of adults. For the combined 7,070 patients, the proportion was 10.6 per cent. Members of a control group comprising 1,024 nurses, medical students, and medical in-patients were questioned, and those reporting some abnormality of birth (rarely associated with brain injury) formed 6.3 per cent of all persons, and 8.7 per cent of the 751 who knew their birth history.

TABLE 2

DISTRIBUTION OF PRINCIPAL CAUSES OF SEIZURES WITH REFERENCE TO PATIENT'S AGE AT THE INITIAL ATTACK

Cause	*Age in Years at Onset of Seizures*							*Total*	*Per Cent*
	–1	1–4	5–9	10–19	20–29	30–49	50+		
Total prenatal	24	25	10	9	1	2	0	71	13.3
Congenital	13	5	4	6	1	1	0	30	5.6
Premature	11	20	6	3	0	1	0	41	7.7
Natal	53	54	33	18	3	0	0	161	30.1
Postnatal trauma	4	28	21	34	15	7	2	111	20.7
Total infection	32	30	15	10	4	0	1	92	17.2
Infection	18	24	14	9	3	0	1	69	12.9
Febrile	14	6	1	1	1	0	0	23	4.3
Other conditions	4	7	4	7	8	1	3	34	6.4
Tumor	0	0	0	2	6	1	0	9	1.7
Circulation	1	1	1	1	1	0	3	8	1.5
Miscellaneous	3	6	3	4	1	0	0	17	3.2
Unknown	12	22	14	11	4	3	0	66	12.3
Total	129	166	97	89	35	13	6	535	100.0
No. per year	129	41.5	19.4	8.9	3.5	0.6			

DISTRIBUTION OF CAUSES IN THE PRESENT SERIES

Table 2 gives more detailed data than table 1 on the causes of epilepsy in our present series, and also includes the 66 cases in which origin of the cerebral lesion could not be determined. The percentage distribution of the 535 cases appears in the last column. Percentages are smaller than in table 1 because of the inclusion of "unknown" cases. Prenatal conditions account for 13.3 per cent; natal for 30.1 per cent; postnatal trauma for 20.7 per cent; infections for 17.2 per cent; other conditions for 6.4 per cent; and "cause not determined" for 12.3 per cent.

A breakdown of these groups follows: The 30 cases grouped under congenital include: cerebral atrophy, eight; agenesis, four; hydrocephalus and congenital syphilis, each three; microcephaly, Sturge-Weber syndrome, and erythroblastosis, each two; and amaurotic familial idiocy, mongolism, myoclonus epilepsy, cretinism, arteriovenous aneurysm, and congenital heart disease, each one. Prematurity occurring in 41 cases was classified as a prenatal cause under the thesis that early expulsions are usually due to unpropitious conditions within the uterus. Thirty-five of the 41 newborn gave evidence of distress at birth.

The 161 babies with complications at birth, representing 30.1 per cent of the total, included anoxia or actual trauma with neurologic deficit of paresis or later spasticity. The labor might have been prolonged or breathing delayed. The events were often complicated or details of the history lacking so that explicit assignment of the blame was not feasible.

Postnatal conditions included 237 cases, or 44.3 per cent of the total. Of these, trauma was most important, occurring in 111 cases, or 20.7 per cent of the total.

Infectious diseases are important because of the possible serious sequelae. Microörganisms find the immature brain and meninges a favorable culture media. Damage done to nerve cells at this time of life may have an effect over the remainder of the person's existence. Among the 69 persons with chronic epilepsy presumably due to infection and organic involvement of the brain, a virus was responsible in 20. Of these, measles accounted for eight cases, postvaccinial encephalitis for six, mumps for two, and some unknown virus for four. Various types of meningitis accounted for 15 cases. Of these, the bacterial agent was unknown in eight, influenzal in six, and pneumococcal in one. Of the 34 persons with other infections, 18 had pertussis, eight had some upper respiratory infection, four had mastoiditis, two had polio, and one had brain abscess or peritonitis. The 23 children with febrile convulsions constituted 4.3 per cent of this total group of acquired epilepsies. Patients were included in this febrile group only if a cerebral lesion followed the febrile convulsion or convulsions and no other etiologic factor could be determined. A detailed analysis from our seizure unit of the significance of febrile convulsions has been published.[9]

Tumor of the brain was demonstrated in only nine persons, 1.7 per cent, all of these young adults. Glioblastoma multiforme was responsible in two cases, and meningioma, astrocytoma, ependymoma, and hemangioma in one each. In the three remaining cases the type was unknown.

Miscellaneous conditions were present in 17 patients; three of anesthetic anoxia; two each of lead poisoning, porencephalic cyst, and allergic response to immunization; one case each of electric shock, illuminating gas anoxia, eclampsia, Heller's disease, diabetes, Sydenham's chorea, Huntington's chorea, and eosinophilic granuloma.

In this study cerebral pathology was attributed to rupture, thrombosis, or arteriosclerosis of cerebral blood vessels in only eight cases. Hemorrhage as a result of trauma or birth injury was included under those items.

Diagnostically the most perplexing group comprises the 66 persons, 12.3 per cent of the total, who displayed evidence of intracranial pathology for which a cause could not be determined. As shown in a succeeding chart, the electroencephalogram or pneumoencephalogram might point to a lesion, but the history failed to provide a cause. Intrauterine mishaps may have been at fault; early febrile convulsions may have been forgotten or have occurred when the child was unobserved. Again, pathologic changes might be the result rather than the cause of chronic epilepsy.

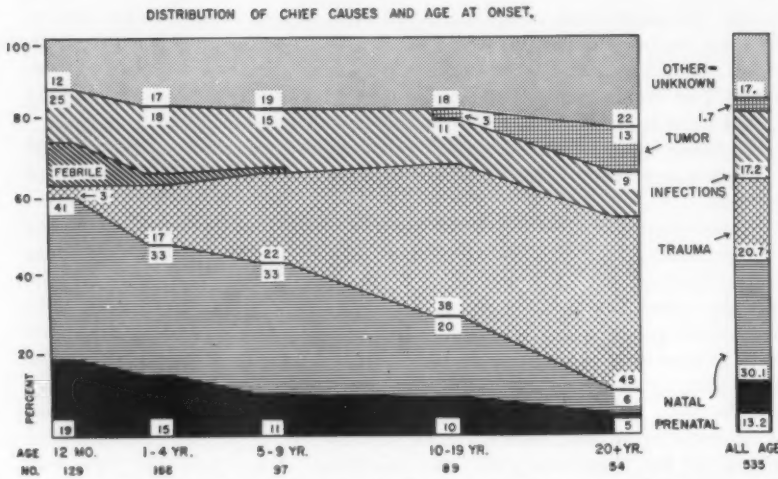


FIG. 1. Distribution of chief causes of pathologic changes on the basis of the patient's age at the initial seizure. Periods of time and the number of patients are indicated below the chart. Figures within the chart refer to percentages in each period of time.

AGE AT ONSET

Table 2 separates patients according to age at the time of the first seizure, including any febrile convulsion. These age periods are variable in length. The relatively high incidence of acquired epilepsy in the early years is demonstrated, and the representation per year, ranging from 129 cases in the first 12 months to 0.6 cases per year for the years 30 through 49, is given. Pathologic changes of unknown origin is distributed through all years but is relatively prominent in later years.

Figure 1 depicts graphically the distribution of causes of epilepsy in the six groups noted in table 1, giving the percentage of causes in each age group. Thus in the first 12 months causes were: prenatal 19 per cent, natal 41 per cent, infections (including febrile) 25 per cent, and miscellaneous (including cause unknown) 12 per cent. Most striking, but not surprising, is the declining importance of paranatal conditions and the increasing importance of postnatal trauma with increasing age.

The relative importance of an early onset of seizures may be shown differently. Of the 30 cases with congenital cause shown in table 2, 18 or 60 per cent began to convulse before the age of five. This proportion for prematurity is 76 per cent, for birth difficulties 66 per cent, for postnatal trauma 29 per cent, for cerebral infections 63 per cent, and for febrile convulsions 87 per cent.

The distribution of causes which totals 100 per cent in each age group, shown in figure 1, does not display the preponderance of a youthful onset.

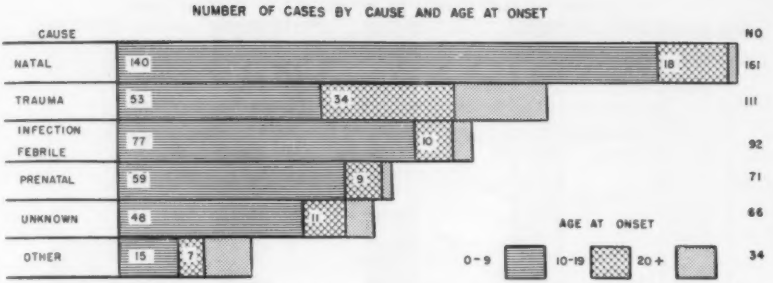


FIG. 2. Numbers of patients with reference to the cause of pathologic changes and age of the patient at the initial seizure.

The causes for the total group, expressed in numbers of cases and not in percentage of a total, are shown in figure 2. The six causes are arranged in order of frequency and three periods of onset. Tumors are included and cases of unknown etiology excluded from the miscellaneous groups. The number of patients with onset at 20 years or later may be derived by subtraction of numbers inside the bars of figure 2 from the total at the end. The percentage distribution of the total numbers appears in the last column of table 2. During the first decade of life (represented in figure 2 by horizontal line), natal conditions are most important, followed by infections and fever, and then by prenatal conditions. Postnatal trauma ranks fourth, although for epilepsy beginning at any age it stands second.

INTERVAL BETWEEN INJURY AND EPILEPSY

The interval of time which separates an insult to the brain and the initial seizure is of much interest. The likelihood of seizure resulting from such damage is increased if the time interval is short. Yet we know from such accurately-dated events as penetrating wounds of the brain in war that the interval may be measured in years rather than days or months. Explanation of this delay is oftentimes difficult. Parents are loathe to believe that birth injury might account for attacks which begin in puberty or later.

Etiologies are obscured when the initial injury is followed later by a second injury. This occurred in 41 of the 435 cases in which the interval could be timed. The interval between the first injury and the onset of seizures was, of course, greater than that between the second injury and the onset. However, the following figures are concerned only with the first injury. Time intervals between insult and seizure for the four principal groups of causes are expressed graphically in figure 3. In nearly one-half, namely 46 per cent, the first seizure occurred within a year after the causative event; 19 per cent occurred in the subsequent two years, eight per cent in the next two years, 15 per cent in the following five years, and 12 per cent after ten or more years had passed. In a few cases the interval was more than 20 years. The

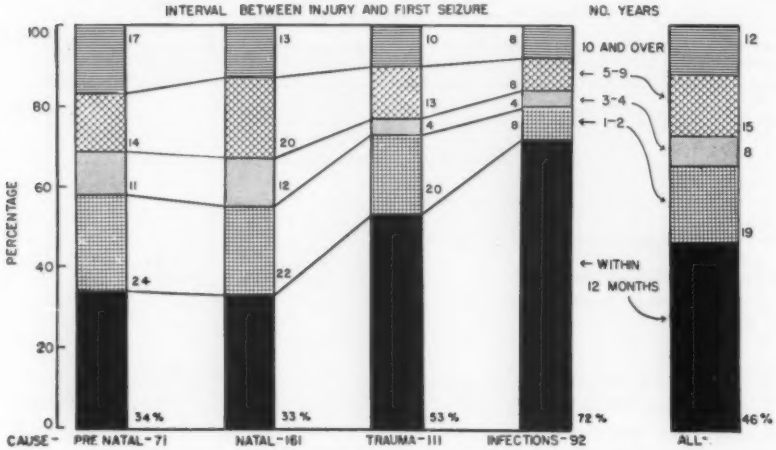


FIG. 3. The time interval in years between the primary brain lesion and the initial seizure with reference to cause of the lesion in 435 cases. The total number of cases is indicated below, and percentages are shown beside each column.

time intervals of the chart are variable. If expressed as percentage per year, there were 46 per cent in the first year, 9.5 per cent in each of the two following, 4 per cent in each of the next two, and 3 per cent in each of the next five years. The proportion having an initial seizure in the year subsequent to the damage was least for the children with natal pathology, only 33 per cent, and highest for infections including febrile convulsions, 72 per cent. Epilepsy that started ten years or more after the original injury was encountered most often in the prenatal group, 17 per cent, and least often in the infectious group, eight per cent. Of the 41 cases with a secondary cause for seizures, initial causes were prenatal or natal in 39.

SOURCES OF EVIDENCE FOR DIAGNOSIS

As stated earlier, evidence for acquired conditions was derived from five sources. Figure 4 shows the relation of these sources not only with respect to the total number of patients examined, but also with reference to the main cause of the acquired condition. In general, the patient's history was most important, giving positive evidence in 470 of the 535 cases, or 88 per cent. Next was the electroencephalographic examination which provided evidence of abnormality in 79 per cent, usually as localized seizure discharges or slow spike-wave formations. Focal features of seizures were present in 51 per cent, and abnormal neurologic signs in 50 per cent of the patients. The pneumoencephalogram indicated abnormalities in 17 per cent. However, this examination was carried out on only a small minority of patients, those with other evidence suggesting a localized pathology. A freer use of this procedure as

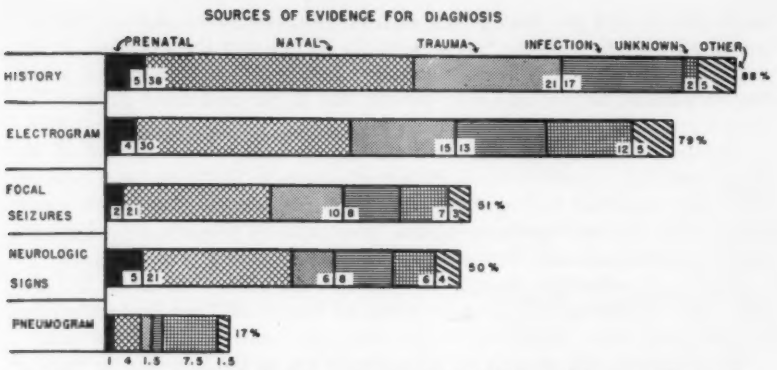


FIG. 4. The sources of evidence in favor of an acquired brain lesion and its cause. Figures refer to percentages.

well as of spinal fluid examinations, films of the skull, subdural taps, and angiograms would doubtless have increased the number of cases deemed primarily organic and brought the diagnosis of proven cases into sharper focus.

As seen by inspection of figure 4, the patient's past history, electroencephalogram, and neurologic examination were especially important in the diagnosis of mishaps at birth. A history of focal seizures was especially important in birth conditions and postnatal trauma. In contrast, the electroencephalogram and pneumoencephalogram most frequently signaled cerebral lesions for which no cause could be found.

As stated earlier, much uncertainty attended the diagnosis of some anatomic changes and the assignment of a cause for it. The proportion of cases in which the evidence for a cause seemed certain varied as follows: prenatal 43 per cent; natal 54 per cent; postnatal trauma 40 per cent; infections 63 per cent; miscellaneous conditions 50 per cent; and all cases (including the unknown which was, of course, zero) 52 per cent.

DISCUSSION

This study of 535 non-institutionalized persons of various ages and economic status emphasizes the wide diversity of conditions, both genetic and acquired, which either alone or in combination may result in some of the various manifestations of epilepsy. This relatively small sample cannot be projected on the general population of epileptics nor can it be adequately compared with reports from other centers of work. Better coordination of viewpoints and of methods of diagnosis is needed. The relative importance of heredity and acquired conditions is being approached by study of data from epileptic twins.[10] These now number 160 pairs.

SUMMARY AND CONCLUSIONS

Records of 1,648 patients with a diagnosis of epilepsy were reviewed. Of

these, 535, or 32.4 per cent gave evidence of organic lesion of the brain acquired prior to the person's first seizure. In 52 per cent the evidence for the pathologic change was believed conclusive, in 48 per cent only probable. Of the 535 patients, 69 per cent were private and 31 per cent clinic patients, the latter being adolescent or younger.

Ninety per cent of patients had the first seizure before the age of 20; 24 per cent had a positive family history of epilepsy. Evidence for a cerebral lesion was furnished in largest proportion, 88 per cent, by the patient's past history, with the electroencephalogram, description of seizures, neurologic examination, and pneumoencephalogram following in order of importance.

Causes of pathologic change were assigned as follows: prenatal 13.3 per cent; natal conditions 30.1 per cent; postnatal trauma 20.7 per cent; infections 17.2 per cent; other conditions 6.4 per cent; and unassigned 12.3 per cent.

Data studied with respect to the patient's age at the first seizure showed a progressive decline of paranatal mishaps and progressive increase of postnatal traumatic conditions with increasing age. Nearly one-half of the cases, 46 per cent, had the initial seizure within 12 months after the first etiologic event. In 12 per cent epilepsy did not arise until ten or more years later. The time interval separating etiology and epilepsy was shorter for postnatal trauma and infections than for paranatal conditions.

The distribution of causes differs radically from a previous series of older patients.

A comparison and coalescence of data from various sources with delineation of genetic and acquired factors is desired.

REFERENCES

1. Stein, C.: Hereditary factors in epilepsy, Am. J. Psychiat. 12:989, 1933.
2. Lennox, W. G.: The multiple causes of seizure in the individual epileptic patient, New England J. Med. 209:386, 1933.
3. Bridge, E. M.: Epilepsy and Convulsive Disorders in Children, New York, McGraw-Hill Book Company, 1949.
4. Peterman, M. G.: Convulsions in childhood, Am. J. Dis. Child. 72:399, 1946.
5. Courville, C. B., and Marsh, C.: Neonatal asphyxia: Its encephalic residuals and mechanism of their production, Bull. Los Angeles Neurol. Soc. 9:121, 1944.
6. Schreiber, F.: Dyspnea of the newborn and associated cerebral injury, J.A.M.A. 111:1263, 1938.
7. Keith, H. M., Norval, M. A., and Hunt, A. B.: Neurologic lesions in relation to the sequelae of birth injury, Neurology 3:139, 1953.
8. Alström, C. A.: A study of epilepsy in its clinical, social and genetic aspects, Acta psychiat. et neurol. Supplement 63, 1950.
9. Lennox, W. G.: The significance of febrile convulsions, Pediatrics 11:341, 1953.
10. Lennox, W. G.: The heredity of epilepsy, as told by relative and twins, J.A.M.A. 146:529, 1951.

Effects of Vasodilatation on Electroencephalograms of Unanesthetized Humans

A. Morello, M.D., S. Merlis, M.D.
and I. S. Cooper, M.D.

THE relationship of effects of vasodilatation to electroencephalographic changes in human subjects has only been given passing attention in the literature. Extensive work has been done on experimental animals,[1,2] and some limited investigations on anesthetized humans have been carried out. It is generally accepted that brain waves are altered by changes in the chemical composition of the blood, while circulatory changes are usually of secondary rather than primary importance. Changes in circulating blood flow, not extensive enough to produce changes in consciousness, have relatively little influence on brain waves.[3] The purpose of the present study is to re-evaluate the relationship of cerebral vasodilators to changes in brain wave patterns in unanesthetized humans.

MATERIAL AND METHODS

Studies were carried out on 45 subjects of both sexes varying in age from 20 to 76, with the majority falling into the 30 to 50 year age group. The individuals were physically normal but chronically ill with various mental disorders. To obtain a standard baseline tracing, resting electroencephalograms were taken a few days before the investigation was carried out, using 18 electrode placements. Two parallel investigations were conducted. In the first group of 30 patients (hereafter referred to as group 1) papaverine hydrochloride in dosages of 46 to 97 mg. (grains ¾ to 1½) and Paveril phosphate in dosages of 130 to 195 mg. (grains 2 to 3) were used. The respective drugs, diluted in 6 to 14 cc. of 5 per cent dextrose in water, were injected intravenously, each injection being preceded by a control injection of 6 to 14 cc. of 5 per cent dextrose in water. These injections were made rapidly within 30 to 60 seconds. In the second group of 15 patients (hereafter referred to as group 2) Paveril phosphate was used in dosages ranging between 3 to 10

From the department of neurological surgery, New York University-Bellevue Medical Center, and the New York State Hospital, Central Islip, Long Island, New York.

grains. The drug, diluted in 500 cc. of isotonic saline, was injected intravenously using a three-way stop cork attached to a 50 cc. syringe. The duration of the injection was about 12 minutes.

In both groups electroencephalographic tracings were taken before, during, and after injection of the drug and of the control solution. The patient's clinical responses were noted carefully. Blood pressure, pulse, and respirations were recorded at frequent intervals throughout the entire study. Electrocardiographic tracings were also recorded continuously during each study.

RESULTS AND COMMENT

In group 1, electroencephalographic changes were observed in 12 cases (36 per cent), consisting of increased voltage of the alpha rhythm and a more stabilized rhythm (figure 1). Delta activity was not present in any of these cases before or following the injection. Moderate tachycardia occurred in

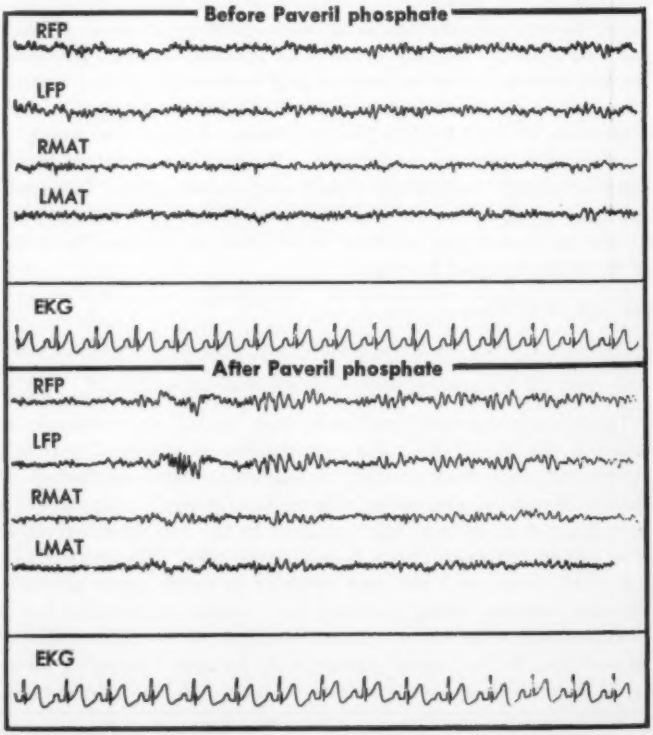


FIG. 1. Electroencephalograms before and after intravenous injection of 195 mg. (grains 3) of Paveril phosphate.

three cases following injection. Changes in the electroencephalogram were found with both vasodilator drugs in equal proportions and could not be correlated with changes in blood pressure, pulse, or respirations. There were no cases in which the systolic blood pressure fell more than 15 mm.

In group 2, the electroencephalographic record showed changes in four cases (26.6 per cent), consisting of minimal decrease in amplitude of the alpha waves in one case and in slight increase in the other cases. In this group electrocardiogram, blood pressure, pulse, and respiratory changes were insignificant and showed no relation to the electroencephalographic changes.

Results of this investigation seem to concur with those in experimental animals and human anesthetized subjects. We have been unable to detect any significant or consistent variation in the electroencephalographic patterns as they relate to the vasodilator effect. Evidence of vasodilation of the cerebral vessels after use of papaverine[4] and Paveril[5] has been demonstrated in different ways. We are inclined to believe that the electroencephalogram is not an adequate method for determining vasodilator effects in the cerebral circulation.

Figure 2 shows angiograms taken before and after intravenous injection of 120 mg. (grains 2) of Paveril phosphate. In the same case 640 mg. (grains 10) of Paveril was injected without any electroencephalographic change, thus

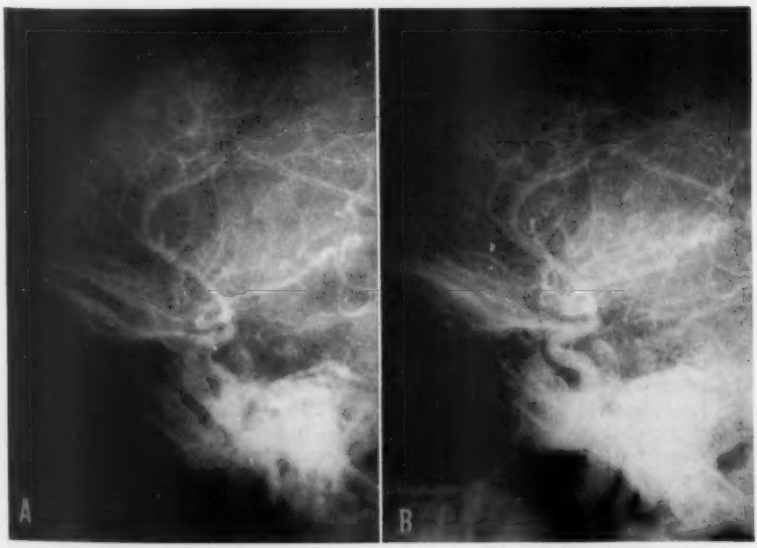


FIG. 2. Carotid arteriogram before (A) and after (B) intravenous injection of 120 mg. (grains 2) of Paveril phosphate.

demonstrating that agents known to produce vasodilatation do not alter the electroencephalogram significantly.

CONCLUSION

Investigations into the effects of large doses of two vasodilator agents (papaverine and Paveril) on the electroencephalogram were made in 45 subjects. No significant changes were noted in the electroencephalogram, although objective evidence of vasodilatation was seen in many of these patients by angiographic technics. It is concluded that the electroencephalogram is not significantly altered by moderate vasodilatation of the cerebral blood vessels.

Drugs kindly supplied by Dr. Kenneth Kohlstaedt of the Eli Lilly Research Laboratories, Chicago.

REFERENCES

1. Thiesen, J. W.: Slow waves of circulatory origin in electroencephalogram, J. Psychol. 15:253, 1943.
2. Gibbs, F. A., Maxwell, H., and Gibbs, E. L.: Volume flow of blood through the brain, Arch. Neurol. & Psychiat. 57:137, 1947.
3. Cobb, S., and Lennox, W. G.: Cerebral circulation: Intrinsic control and clinical phenomena, Federation Proc. 7:151, 1944.
4. Shenkin, H.: Effects of various drugs upon cerebral circulation, J. Appl. Physiol. 3:465, 1951.
5. Cooper, I. S., and Morello, A.: Intracarotid injection of papaverine in cases of cerebrovascular thrombosis, J. Neurosurg. 10:331, 1953.

It may be urged that in idiopathic epilepsy the affection of the two sides is synchronous, and that therefore there cannot be a passage of the discharge from one hemisphere to the other. But the instantaneous involvement of all the muscles of one side may occur from spread of discharge. In some cases minor attacks begin locally and spread slowly, and severer attacks seem to begin simultaneously in all the muscles. In the latter case we are justified in assuming that there is a spread of discharge through the centres, which occurs too rapidly to be observed. There is no greater difficulty in admitting the instantaneous spread of an intense discharge to the opposite hemisphere than in admittting its extension through the centres of one hemisphere. So rapid is the transmission of nervous impulses, that centres structurally connected by fibres which extend from one hemisphere to the other may be in as intimate functional connection as centres which lie in juxtaposition. Luciani's experimental demonstration of what may occur in a mutilated brain does not prove that the process is always the same when the hemispheres are intact.

That this theory of the process of the epileptic fit is correct, is, I think, proved by a very important case which has been lately published by Oebeke, and which also, as its narrator points out, is of not less value from the evidence which it affords that the convolutions are the seat of the discharge in idiopathic epilepsy. A patient who had been liable to general epileptic fits from birth was seized, in adult life, with left hemiplegia, due, as was afterwards discovered, to a haemorrhage in the central ganglia of the right hemisphere. The epileptic fits continued to occur after the onset of the hemiplegia, but affected only the unparalyzed side.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Clinical Evaluation of Pagitane Hydrochloride in Parkinsonism

Robert S. Dow, M.D. and Gordon N. Smith, M.D.

WELL OVER A CENTURY has passed since Parkinson first described the clinical entity which bears his name. In 1817 he wrote: "Although at present uninformed as to the precise nature of the disease, still it ought not to be considered as one against which there exists no countervailing remedy. On the contrary, there appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped."[1]

In the intervening years various disease entities were found to cause the clinical picture, and we now speak of Parkinson's syndrome and Parkinson's disease. Parkinson's disease, paralysis agitans, is the result of progressive primary neuronal degeneration. Parkinson's syndrome, or parkinsonism, includes not only cases of paralysis agitans, but also those whose clinical picture is the result of arteriosclerosis, encephalitis, and the infrequent instances which follow as a result of neurosyphilis, brain tumor, and toxic agents.[2,3]

Therapy of this disease remains essentially that of palliation and consists of the use of drugs which, selective in their action on the nervous system, accomplish some measure of control of the rigidity and tremor of this condition. Alkaloids of the belladonna group have long been used and are effective to some degree. More recently attention has been directed to synthetic compounds whose effect on the central nervous system is greater and whose side reactions of dryness of the mouth and blurring of vision are often less troublesome. Among these synthetic compounds is trihexyphenidyl or Artane. Various antihistamine compounds, particularly those with a sedative effect, are also valuable.

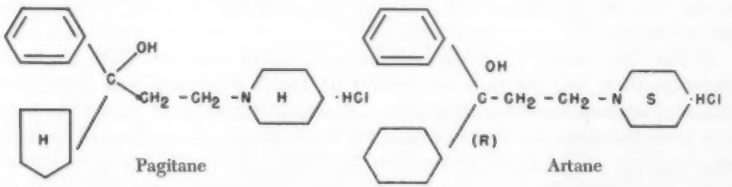
In 1949 the results of treatment of a small group of patients with a new synthetic drug, Artane, was reported.[4] Our conclusions at that time were: 1) that Artane resulted in definite improvement in the rigidity and tremor of eight out of ten patients with parkinsonism, all of whom were subjected to control study and observation before and after its use; 2) that in some cases it appeared to be superior to other medication, but was found most useful in con-

From the division of neurology, department of medicine, University of Oregon Medical School, Portland.

junction with older preparations; 3) that the drug deserved an important place in the treatment of parkinsonism and should be given a clinical trial in every case. Subsequent clinical use and the experience of others have confirmed these observations.[5–11] In our opinion Artane has been the drug of choice in the control of the symptoms of the parkinsonian syndrome.

During the past year another new synthetic compound has been available to us for clinical trial. Having been convinced by controlled studies as reported previously that Artane was more effective than naturally occurring drugs of the belladonna group in the majority of patients, it was felt that this new drug could best be tested by comparing it with Artane in dosage, effectiveness, and side effects. A few of the patients reported in this study were among those used in the original evaluation of Artane.

This newer drug, an aminopropanol, is known as Pagitane hydrochloride (cycrimine hydrochloride). Inspection of its formula shows that it is structurally unlike the belladonna alkaloids, but has some resemblance to the structural formula of Artane and represents another new therapeutic approach.



Extensive preliminary tests for evidence of chronic toxicity have been conducted on dogs, rabbits, rats, and mice. The compound is slightly but not impressively more toxic than atropine in mice and rats by either oral or intravenous administration. Pharmacologically the compound demonstrates antispasmodic activity on the intestine, exhibiting an activity approximately equal to that of atropine on isolated guinea pig intestinal strips stimulated with Mecholyl or acetylcholine. Very little antihistaminic activity was shown on similar test preparations. Other tests were carried out using Thiry fistulas in dogs, uterine muscle from guinea pigs, salivary flow, and the cardio-inhibitory effect in cats.

MATERIAL AND METHODS

The present study was begun in October 1952. The clinical material on which this report is based consists of 23 patients in all, about equally divided between out-patient clinic and private patients. There were 18 men and five women ranging in age from 28 to 77, with an average age of 63.5 years. Six had postencephalitic parkinsonism, nine cases were considered to be idiopathic in form or true paralysis agitans, four were arteriosclerotic in type, one was posttraumatic in etiology, one was a case of cerebral arteriosclerotic spasticity and not truly a case of Parkinson's syndrome, one had a violent tremor

of the hand and arms not typically parkinsonian but occurring in an elderly arteriosclerotic woman of 73 years, and one was a case of spasmodic torticollis.

Ten patients were studied before and after substituting the new drug for Artane by the following methods: 1) accurate determination of the time necessary to button a laboratory coat and to lace and tie a shoe, 2) electromyography, 3) motion pictures before and after Pagitane hydrochloride was substituted for Artane, 4) subjective evaluation by the patient, 5) estimation of tremor and rigidity by clinical examination. Blood counts and urinalyses were obtained in ten patients at two-week intervals during the first month of therapy, and at monthly intervals thereafter.

RESULTS

In only two patients of the group was there a significant change in the time requirement for buttoning the laboratory coat; one took longer on the new drug and the other less time when compared with ability in that regard while on Artane. In the ten patients who were compared as to the time required to lace a shoe, all could accomplish this in less time when given Pagitane hydrochloride than when on their previous dose of Artane. The electromyograms were not considered of much value in comparing improvement before and after administration of the new antispasmodic. In only one case was there any change, and here there was marked improvement in the record taken after the new drug was used.

TABLE 1

RELATIONSHIP OF ETIOLOGY TO PATIENT IMPROVEMENT

Etiology	*No. of patients*	*Subjective improvement*				*Objective improvement*			
Parkinsonism due to:		3+	2+	1+	0	3+	2+	1+	0
Postencephalitic	6	1	1	3	1	0	1	3	2
Paralysis agitans	9	3	4	2	0	0	3	5	1
Arteriosclerotic	4	0	0	3	1	0	0	1	3
Posttraumatic	1	0	0	1	0	0	0	0	1
Cerebral arteriosclerotic spasticity	1	0	0	0	1	0	0	0	1
Violent tremor in an arteriosclerotic	1	0	0	0	1	0	0	0	1
Spasmodic torticollis	1	0	0	0	1	0	0	0	1
Total	23	4	5	9	5	0	4	9	10

Table 1 illustrates the drug's relative effectiveness among patients classified according to supposed etiology. It will be noted that subjective evaluation was higher than was noted objectively and that in general the arteriosclerotic patients did very poorly on the compound.

Subjective improvement, rated arbitrarily from 3 plus to 0 rating and based upon the patients' appraisal of the relative effectiveness of the two drugs,

showed 3 plus subjective improvement in four patients, 2 plus in five patients, 1 plus in nine, and no change in five.

Our own impression based on clinical observation of the severity of symptoms indicated that four showed 2 plus improvement, nine demonstrated 1 plus improvement and nine showed no objective change over their condition than when on Artane. One reported only by letter and did not return for a follow-up examination and evaluation of the results of therapy.

Blood counts and urinalyses were obtained in ten patients. One showed a transient neutrophilic leukopenia which returned to normal without discontinuing the drug; it was thought not to be related to the medication. In one patient leukocytes were found in the urine, but again this was not considered to be the result of medication.

The dosage most commonly showing 2 and 3 plus subjective improvement was a 5 mg. tablet 5 times daily.

ADMINISTRATION

In almost all patients the drug was increased gradually, beginning at a dosage of 7.5 mg. daily in divided doses and increasing until side reactions were obtained. Included in the side reactions were the following: dryness of the mouth in ten, constipation in nine, blurring of vision in seven, mental confusion in three, headache in one, unsteadiness or weakness in walking in three, difficulty in swallowing in one, and blepharitis and conjunctivitis in one.

TABLE 2
EVIDENCE OF OVERDOSAGE

Symptoms	*No. of patients*
Dryness of mouth	10
Constipation	9
Blurring of vision	7
Mental confusion	3
Headache	1
Unsteadiness or weakness	3
Difficulty in swallowing	1
Blepharitis and conjunctivitis	1

The drug has been discontinued in ten patients. Two patients stopped the new medication because of mental confusion; both of these were over 70 years of age and had marked cerebral arteriosclerosis. In two more patients the drug had to be discontinued because of weakness and unsteadiness; one of these patients had cerebral arteriosclerosis without true parkinsonism, but showed rigidity, spasticity, and pseudobulbar symptoms; the other was a case of postencephalitic parkinsonism who preferred Artane and asked to go back to its use. Another patient whose medication had to be changed had cerebral arteriosclerosis, and developed a very severe headache while on the new drug.

Constipation became so severe in one case of paralysis agitans that the Pagitane hydrochloride had to be stopped. Another patient developed conjunctivitis and blepharitis, but subsequently asked to be put back on the drug and is now taking it. A stroke ended the life of another man with cerebral arteriosclerosis. Two patients failed to return for adequate follow-up study, and the medication was discontinued.

A favorable response to Pagitane hydrochloride is illustrated by the following case:

A 63 year old woman was first seen on July 12, 1933, and was first treated in 1935. She had severe sleeping sickness in 1923 and was ill for six months. She had double vision, severe headache, and tremor starting in the right hand about two years before she was seen in the clinic in 1933, ten years after onset of sleeping sickness. She was started on scopolamine hydrobromide and was seen at fairly regular intervals. She continued at various times taking scopolamine hydrobromide, phenobarbital, and stramonium. Finally in December 1948 she was started on Artane, 2 mg. five times a day, plus a scopolamine mixture. Throughout the subsequent years she felt that this was her most effective medication. One note made in 1949 stated that while taking both Artane and scopolamine the patient was much better than she had been for years. She continued to be well satisfied with her medication until December 1952, when she felt that her tremor was getting worse.

The patient was started on Pagitane hydrochloride, 2.5 mg. four times a day. She reported marked improvement from the beginning, with no blurring of vision, loss of appetite, constipation, or other side effects. Her dose was then increased to 15 mg. daily in divided doses, with still no side effects. She claimed that at times the tremor stopped entirely, and the dosage was increased to 20 mg. daily in divided doses. Her improvement has continued, and she is the most enthusiastic patient we have on this medication. The use of scopolamine has been omitted entirely, and the patient's tremor is well controlled on the present dose.

The only side effect is constipation. Blood counts and urinalyses are normal. The electromyogram before and after medication showed no change; it was abnormal and characteristic of Parkinson's disease. Subjective improvement was rated 3+, objective improvement 2+.

Summary: This patient with typical postencephalitic parkinsonism of many years' duration had received more benefit from Artane than from any previous medication. She was able to tolerate almost double the dose of Pagitane hydrochloride without uncomfortable side effects, and considerable improvement was achieved over the previous effective dose of Artane.

Another case illustrates an unfavorable response to Pagitane hydrochloride:

A 71 year old man was first seen on January 15, 1953, with the diagnosis of cerebral arteriosclerosis and parkinsonism of arteriosclerotic origin. He complained of having had heart disease since 1940, episodes of mental confusion for several years, and a parkinsonian tremor for one year. He was started on Artane, one 2 mg. tablet a day, but while it helped his shaking immediately, he was slowed down mentally. His legs became weak and he had difficulty with speech. The dose was then cut to half a tablet three times a day, but he became quite forgetful under this medication. At this time he was given a supply of the Pagitane hydrochloride, and advised to begin with half a tablet three times a day. When he reported on March 11, 1953, he was still mentally confused and was advised to discontinue the drug entirely. He was then given Benadryl, 50 mg. three times a day, which seemed to help him considerably, without the side reactions of mental confusion which he found so objectionable when taking Artane and the new compound.

Summary: This patient with arteriosclerosis and arteriosclerotic heart disease, who had some mental confusion prior to the administration of these drugs, reacted unfavorably to both Artane and the Pagitane hydrochloride. Side effects of mental confusion and forgetfulness occurred while he was taking these medications, so it was not deemed advisable to use these drugs for this patient. He had a reasonably good response to Benadryl alone.

DISCUSSION

Corbin[7] has aptly phrased the difficulties of evaluating a compound by these methods: "In the evaluation of a new drug in the treatment of any disease, especially in parkinsonism, it is well to bear in mind that chronically ill patients, no matter how critical or objective they try to be, are biased in favor of the new medication. If the drug produces any euphoria or alteration in mental state, it is well nigh impossible to rely on the subjective impressions. And if the physician is convinced of the new drug's effectiveness, his enthusiasm alone may produce a transient benefit all too often ascribed to the medication which he unconsciously is 'selling.'"

It is known that the rigidity, tremor, and weakness of parkinsonism are modified by environmental temperature and the emotional state of the individual. Generally speaking, cold and inactivity make the patient more rigid, and emotional tension will increase his tremor and salivation.

Thus it is seen that appraisal of therapeutic results in parkinsonism is open to a wide range of interpretation, since the patient's reaction is predicated on many factors, some of which are beyond the rigid control of the examiner.[8] It is desirable, therefore, in reporting the value of any treatment in such chronic and long continued illness, to refrain from overenthusiastic conclusions based on one small cross-section of time or series of cases. Many times the initial effect of the drug appears remarkable, but the improvement tends to lessen with time. Experience teaches that patients react differently to any drug, depending upon the type, duration, and the degree of illness, age of the individual, temperament, mental attitude, and constitutional make-up. Since the aim of treatment in parkinsonism is not only to achieve physical improvement but also to bring greater contentment and peace of mind to the patient, it is obvious that the less unpleasant the side reactions produced by the medication, the better cooperation and results can be obtained.

CONCLUSIONS

Irrespective of all the pitfalls of an analysis such as this on a relatively small number of patients, our experience with this compound has allowed us to formulate the following conclusions which are in general agreement with published reports now appearing on the use of Pagitane hydrochloride.[12,13]

1. This compound is an effective drug in reducing the rigidity and tremor encountered in parkinsonism.

2. It can frequently be given in larger doses than similar compounds previously available, without producing unpleasant side reactions which would necessitate discontinuing medication.

3. A tendency is noted for some of the patients to report greater improvement soon after beginning therapy. This is characteristic of parkinsonism and makes evaluation of the new remedy difficult.

4. As has been noted previously by others, those patients respond poorly to medical management who have parkinsonism appearing late in life, in whom tremor is the predominant symptom, and who have been diagnosed as having central nervous system changes attributable to arteriosclerosis. In these patients, mental confusion is frequently produced and the drug, if used at all, must be given with great caution.

5. Best results were obtained in parkinsonism of idiopathic or postencephalitic etiology.

Pagitane hydrochloride supplied through the courtesy of Eli Lilly and Company.

REFERENCES

1. Parkinson, James: An Essay on the Shaking Palsy, London, Whittingham and Rowland, 1817. (Reprinted by Ostheimer, A. J.: Arch. Neurol. & Psychiat. 7:681, 1922.)
2. Forster, F. M.: Parkinsonism, M. Clin. North America 37:523, 1953.
3. Brenda, E., and Cobb, S.: On the pathogenesis of paralysis agitans (Parkinson's disease), Medicine 21:95, 1942.
4. Dow, R. S., and Rosenbaum, H.: The treatment of parkinsonism with Artane, Northwest Med. 48:699, 1949.
5. Shapiro, S. K.: Drug therapy in parkinsonism, Minnesota Med. 35:1031, 1952.
6. Corbin, K. B.: Trihexyphenidyl: Evaluation of new agent in treatment of parkinsonism, J.A.M.A. 141:377, 1949.
7. Corbin, K. B.: Treatment of parkinsonism and related disorders in general practice, M. Clin. North America 33:1131, 1949.
8. Effron, A. S., and Denker, P. G.: Clinical evaluation of certain antihistaminic and antispasmodic drugs in Parkinson's disease, J.A.M.A. 144:5, 1950.
9. Doshay, L. J., and Constable, Kate: Artane therapy for parkinsonism: Preliminary study of results in 117 cases, J.A.M.A. 140:1317,1949.
10. Schwab, R. S., and Tillmann, W. R.: Artane in the treatment of Parkinson's disease: Report of its effectiveness alone and in combination with benadryl and Parpanit, New England J. Med. 241:483, 1949.
11. Berkowitz, B., and Alvermann, E.: Trihexyphenidyl (Artane), strammonium, and non chemotherapy in paralysis agitans, Arch. Neurol. & Psychiat. 67:462, 1952.
12. Mulder, D. W.: Evaluation of a new agent in the treatment of parkinsonism, Proc. Staff Meet., Mayo Clin. 28:210, 1953.
13. Magee, K. R., and DeJong, R. N.: Antispasmodic compound 08958 in treatment of paralysis agitans, J.A.M.A. 153:715, 1953.

Whatever be the exact nature of the temporary paralysis after convulsion, it is noteworthy that the transient condition of the limbs is precisely similar to the permanent condition in cerebral paralysis. There motor weakness, lowered cutaneous reflex action, excess of the myotatic contractions (tendon-reflexes). When unilateral convulsions occur with great frequency, so that recovery from the weakness caused by one does not occur before another convulsion comes on, a condition of persistent absolute hemiplegia may result, having all the characters of that due to a destructive brain lesion. In a case lately under my care a patient had on three occasions, for about ten days, more than a hundred unilateral fits daily, and complete hemiplegia with inability to speak. On the cessation of each series of fits the hemiplegia passed completely away.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Amyotrophic Familial Spastic Paraplegia

Sigvald Refsum, M.D. and S. A. Skillicorn, M.D.

MANY STUDIES have been made outlining definite syndromes and differentiating various clinical types of hereditary degenerative diseases of the nervous system.[1] But the question has often been raised: Do these syndromes constitute separate entities or merely represent different manifestations of one disease process? An increasing number of authors classify hereditary spastic paraplegia with the hereditary ataxias.[2-5] Also, there is some evidence to suggest a relationship between hereditary ataxia and peroneal muscular atrophy.[6-8]

Occasional reports of transitional and intermediate forms point to a common etiologic denominator of some of these diseases.[9] In certain cases, a "pure" clinical syndrome may be accompanied by additional neurologic abnormalities ordinarily not associated with that particular entity.[10-12] Though rarely, muscular atrophy may be associated with hereditary spastic paraplegia.[13,14] A combined, extensive involvement of upper and lower motor neurones, including those in the medulla, is decidedly rare, especially when onset of the disorder occurs in early childhood. The cases reported here represent such a clinical picture observed in three siblings.

CASE REPORTS

Case 1.—A 22 year old white man complained of generalized muscle wasting and stiffness. He was born six weeks prematurely, but delivery and early development were normal. At age three he had a febrile illness lasting three weeks, followed by a five week period of generalized weakness. The condition was diagnosed as "probable poliomyelitis." He recovered completely. At the age of four he gradually developed a "stumbling" gait, and walked on the balls of his feet. This became progressively worse, until at the age of six partial tenotomy of both Achilles tendons was done. In the following years stiffness and mild weakness of both legs progressed steadily. At the age of nine he required crutches, and at 14 years he was confined to a wheelchair. At 17 his speech became slurred and he had difficulty in swallowing. Gradually weakness and stiffness involved his hands and arms, with progressive wasting of the extremities and "twitchings" of the muscles of the entire body. At 20 the muscle wasting progressed rapidly, and weight loss amounted to 20 pounds in one year. Difficulty in speaking and swallowing and generalized stiffness also became steadily worse, and the patient eventually was confined to bed. At the age of 21 his illness was further complicated by several prolonged, unexplained episodes of diarrhea.

From the department of neurology, University of California School of Medicine, San Francisco.

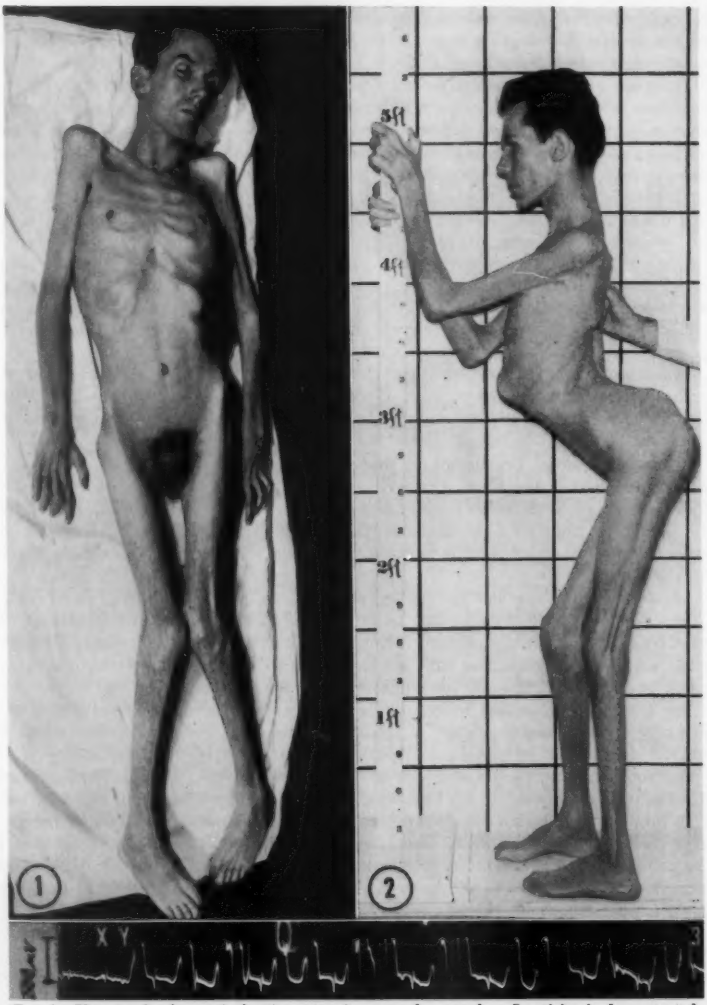


FIG. 1. Photograph of case 1 showing extensive muscular atrophy. Spasticity is demonstrated by the "scissors" attitude of the lower extremities.

FIG. 2. The patient is unable to assume an erect position. The marked lordosis and bony protrusions produce an equine-like stance.

FIG. 3. Spontaneous burst of fibrillations (x) and motor unit (y) action potentials from left brachioradialis muscle, recorded 10 minutes after hypodermic injection of 15 mg. of Prostigmin.

Examination: The patient was bedridden and unable to turn over without aid. He was quiet, oriented, and cooperative. Marked muscle wasting (figures 1 and 2), continuous muscle fasciculations, and severe scoliosis to the right were present, with flaring of the rib

cage and protrusion of the sternum. Any attempt to sit up resulted in hyperextension of the spine. Both feet exhibited fixed pes cavus and hammer-toe deformities. The heart, lungs, and abdomen revealed no abnormalities.

The pupils were of equal size and reacted normally. There was no nystagmus. The fundi were normal. There was a slight flattening of the right nasolabial fold with drooping of the corner of the mouth on that side. The patient had moderate dysphonia and dysphagia. The posterior pharyngeal muscles were weak bilaterally, and there was paresis of the soft palate, especially on the right. On laryngoscopic examination the cricothyroideus and vocalis muscles were seen to be almost completely paralyzed bilaterally. The tongue showed slight atrophy; it protruded in the midline but was weak in lateral movements. The entire body musculature showed extensive atrophy and pronounced decrease of muscle power, most severe in the distal portions of the extremities, with a complete bilateral foot-drop. Nearly continuous fasciculations were present in all muscle groups. Muscular spasticity was generalized but most pronounced in the legs. Uncontrollable spontaneous clonic movements of both lower extremities occurred intermittently, and the slightest stimulation of the legs produced a homolateral mass withdrawal reflex.

The deep muscle reflexes were exaggerated throughout. The jaw reflex was very brisk. The head retractor reflex was positive. The abdominal skin reflexes were normal, while the deep abdominal muscle reflexes were hyperactive. There was no response of the toes on plantar stimulation. Coordination and sensory testing revealed no abnormalities.

Laboratory studies: Routine blood studies and urinalysis were normal; blood serology was negative; serum and urine creatinine and creatine were normal; there were no urine porphyrins. Spinal fluid pressure was 140 mm. of water, with free rise and fall on jugular compression; the spinal fluid contained 4 lymphocytes per cu. mm.; the protein was 40 mg. per cent; Wassermann and Kolmer reactions were negative; and there was a normal colloidal gold curve.

An electrocardiogram and roentgenograms of the skull were normal. Roentgenograms of both feet confirmed the bilateral pes cavus, moderate hammer-toes, and mild hallux valgus which were clinically evident. X-ray films of the spine revealed a rotoscoliosis in the lumbar region, concave to the left, and in the thoracic spine, concave to the right; the lumbar lordosis was increased. All the bones were notably decalcified.

The electroencephalogram was characterized by a mild generalized dysrhythmia of nonspecific type, consisting of occasional random five to seven per second slow waves in all areas.

Electromyography was carried out in all four extremities. Definite fibrillation action potentials were present in the left brachioradialis muscle (figure 3). In all examined muscles a low rumbling noise and flat slow potentials were observed at rest. Isolated motor unit action potentials characteristic of fasciculations appeared fairly frequently; most of these were polyphasic. Abnormal polyphasic motor unit potentials were also seen with voluntary contractions. The muscles in the lower limbs offered an abnormal resistance to the penetrating needle, suggesting fibrosis.

A biopsy from the right deltoid showed small muscle fibers with normal striations and cross-striations. In one small area, however, there was a concentration of nuclei arranged according to the pattern of a muscle bundle without actual muscle fibers present. In another section similar foci of atrophy were found with additional secondary replacement by collagenous fibers and fat.

Psychometric tests revealed an intelligence quotient of 114.

Case 2.—A 17 year old white girl, sister of case 1, complained of generalized weakness and stiffness of her legs. Birth and early development were normal. At the age of five she had a serious febrile illness of unknown nature. Following this, she gradually developed difficulty in walking, characterized by frequent stumbling. Within a year or so the calf muscles became stiff and shortened, and she walked on the balls of her feet. The condition progressed slowly, and at the age of nine she had extreme difficulty

in walking due to bilateral leg stiffness. Finally she had to use crutches. At the age of 15 she noticed that the right calf muscles were gradually lengthening, and eventually she was able to stand with her right foot flat on the floor. At about the same time she became aware of progressive weakness of her hands. When she was tired she had some difficulty in talking. Approximately three months prior to hospitalization she noted a lengthening of the left calf muscles. This was accompanied by muscle twitching in the extremities. Her condition gradually became worse, with increasing stiffness and weakness of her arms and legs.

Examination: General physical examination was entirely normal. The patient was alert, oriented, and cooperative. She walked on the balls of her feet with a characteristic spastic "scissors" gait, and required support in order to walk.

The cranial nerves were normal except for an occasional difficulty in phonation and slight dysarthria. Muscle power was moderately decreased throughout, particularly in the distal portions of the extremities, and both gastrocnemius muscles were almost completely paralyzed. There was slight atrophy of the small muscles of the hands, particularly the first interossei and the hypothenar groups, as well as the tibialis anterior muscles of the legs. Occasional muscle fasciculations could be seen in the small muscles of the hands. Spasticity was extreme in the lower extremities and moderate in the arms. There was sustained bilateral patellar and ankle clonus. The deep muscle reflexes were exaggerated throughout, except for the triceps surae reflexes which were hardly obtainable. Babinski's sign was strongly positive bilaterally. The jaw reflex was increased, and the snout and head retractor reflexes were positive. Coordination and sensory testing revealed no abnormalities.

Laboratory studies: Routine blood studies and urinalysis were normal; blood serology was negative; serum and urine creatine and creatinine were normal; there were no urine porphyrins. Spinal fluid pressure was 160 mm. of water, with free rise and fall on jugular compression; spinal fluid contained no cells and a protein of 57 mg. per cent; Wassermann and Kolmer reactions were negative; the colloidal gold curve was normal.

An electrocardiogram and roentgenograms of the skull and of both feet were normal. Roentgenograms of the spine showed a thoracic scoliosis with convexity to the left, and lumbar scoliosis with convexity to the right.

The electroencephalogram was characterized by a minimal generalized dysrhythmia of nonspecific type, consisting of five to seven per second slow activity which briefly disturbed the record on rare occasions.

Electromyographic studies were made of the muscles of all four extremities. At rest, a good deal of low potential spontaneous motor unit activity was noted, but no fibrillation action potentials were observed. The wasted small muscles of the hands produced high voltage, separated, single motor unit potentials suggesting the dropping out of other motor units. A muscle biopsy from the left tibialis anticus muscles showed no abnormalities.

Psychometric tests revealed an intelligence quotient of 99.

FAMILY HISTORY

The patients' paternal grandmother, suffering from "syphilis of the brain," was confined to an asylum for several years before her death at 48. Nothing was known of the paternal grandfather. The maternal grandfather was in excellent health until he died at age 32 in a railroad accident. The maternal grandmother died from pneumonia at age 80.

The patients' father had "hereditary syphilis," diagnosed on the basis of a positive blood test when he was 34, at which time he gradually lost his vision. He received treatment over a three year period, after which his eyesight returned. He remained well until he died of cancer of the stomach at the age of 62. The patients' mother is active and well at age 61. Serologic tests on the mother's blood were reported as negative. The mother has two brothers and one sister who, together with their children and grandchildren, have had good health.

There were eight siblings, five male and three female (figure 4). The eldest, a male,

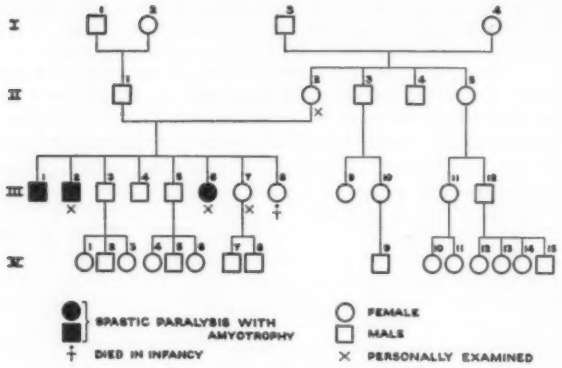


FIG. 4. Diagram illustrating familial incidence in one of four generations.

suffered from a disease described in every respect as identical with that of case 1. This brother developed a stumbling gait at the age of three, followed by slowly progressive weakness, wasting, spasticity, and bulbar disturbances. He was bedridden in the last few years of his life. Death due to respiratory failure occurred at the age of 29.

Two older brothers, when aged 27 and 22 respectively, suddenly fell ill at the same time and in the same locale; both cases were diagnosed as "poliomyelitis." Both had enjoyed good health until that time. The older brother recovered completely, while the younger has retained a slight weakness of his left extremities. Another brother, aged 31, has always been in good health.

One sister died from pneumonia at the age of 15 months, having been healthy until then. The other sister, aged 19, is in good health.

A total of eight children, ranging in age from nine months to 11 years, have been born to three of the healthy siblings and all are well.

The family is of Scottish, Irish, and English extraction. The medical family history was investigated as completely as possible, and no other significant illnesses were uncovered.

DISCUSSION

The clinical course in all three of these cases has been surprisingly similar in every respect. At the time of examination their condition was neurologically indistinguishable from amyotrophic lateral sclerosis. In view of the early onset and relatively prolonged course such a diagnosis does not, however, seem tenable.[15]

Familial incidence of amyotrophic lateral sclerosis has been described,[16-19] but in many of these reports differentiation from hereditary spastic paraplegia is not entirely clear. Koerner[20] recently reported the incidence of amyotrophic lateral sclerosis in natives on Guam. Forty per cent of these cases gave a history of a similar disease in the family; as many as five members in one generation were affected. The earliest age of onset was 26 years.

The initial appearance of the neurologic disorder following an acute systemic illness is not an uncommon occurrence in hereditary diseases;[1, 21] likewise

the age of onset in most cases is similar for afflicted members of the same family (homochromy).[7, 22, 23, 24]

Although a number of cases have been described in which spastic paralysis was associated with amyotrophy, few if any resemble those of this report. Many demonstrated one or more additional neurologic abnormalities, including nystagmus, ataxia, incoordination, intention tremor, macular degeneration, optic neuritis, and mental changes.[2, 3, 11] In those patients not exhibiting additional signs atrophy was much less widespread in most instances,[14] and the onset of the disorder usually occurred at a later age[25] than in the present cases. When examined, case 2 was about the age at which muscular wasting first appeared in her two older brothers. It is anticipated, therefore, that atrophy will be progressive. The electromyographic findings of both patients were interpreted as indicative of a lower motor neuron defect, and the muscle biopsy findings in case 1 were interpreted as representative of neurogenic muscle atrophy rather than changes from disuse or of a dystrophic nature.[26]

In examining these patients, particular care was taken to detect the possible involvement of systems other than the motor. Frequently case reports stress motor findings but ignore other signs of neurologic dysfunction. Many of the reported cases of spastic paraplegia have represented a clinically heterogenous collection of central nervous system disturbances. Still more significant is the fact that necropsy studies of verified "pure" hereditary spastic paraplegia usually show demyelination of the posterior columns in addition to the lateral corticospinal tracts. Some cases also reveal involvement of the spinocerebellar tracts, Clarke's columns, anterior horns, cerebellum, basal ganglia, and rubrospinal tracts, despite clinical evidence of spastic paralysis only. Although autopsy reports of cases of spastic paraplegia are comparatively scarce, most of them reveal that histologic degeneration is usually more extensive than had been expected from the clinical findings.[21, 27]

There is considerable disagreement as to the genetic mechanism of many of the hereditary diseases.[24] In several cases of spastic paraplegia, including those of the present report, recessive heredity is probable.[22] However, dominant heredity has also been implied in a number of reports,[3, 28] while some cases have suggested sex-linked heredity. Landau and Gitt[3] believe that a single dominant gene in association with modifiers is largely responsible for the various phenotypic patterns in some families. Garland and Astley[14] suggest that the amyotrophy was produced by the same gene which was responsible for spastic paraplegia and pes cavus in their cases.

There are three main syndromes which seem to demonstrate clinical transitions and overlap: hereditary spastic paraplegia, hereditary ataxias, and peroneal muscular atrophy of Charcot-Marie-Tooth. Since ataxia indicates a failure of muscular coordination, classification of spastic paraplegia as one of the hereditary ataxias is not plausible. Intermediate forms, however, may reveal both spasticity and incoordination, for which the descriptive term "spastic ataxia" has been used, adding to the confusion by implying the existence of

another distinct entity. Similarly, when spasticity extends beyond the lower extremities, as it did in the cases reported here, the term "hereditary spastic paralysis" might be appropriate; basically, however, spastic paraplegia was the outstanding abnormality, so that designation should be maintained.

Friedreich's disease is the most common of the hereditary ataxias,[29] which comprise a wide variety of clinical disturbances having in common signs referable to some portion of the cerebellar system. Marie's hereditary cerebellar ataxia is a controversial entity, and, as indicated by Critchley and Greenfield,[30] it may be impossible to differentiate clinically between cortical cerebellar degeneration, Marie's hereditary ataxia, and olivopontocerebellar atrophy. All syndromes of this group, nevertheless, exhibit one distinguishing characteristic: ataxia.

The skeletal deformities were a striking feature in case 1. Bell and Carmichael[22] observed that scoliosis was almost universally absent from cases diagnosed as spastic paraplegia; on the other hand, such abnormalities are comparatively common in the hereditary ataxias.[25,31]

Charcot-Marie-Tooth disease rarely is combined with neurologic abnormalities of other entities and only then may it present diagnostic difficulty.

It is suggested that classification of these particular hereditary disorders be made according to the predominant neurologic abnormalities present in the particular case under consideration. Such abnormalities usually are those which also were first to appear clinically at onset of the disease. This was true of the cases reported here, the disorder being initiated by the appearance of spastic paraplegia, which continued as the outstanding feature of the illness despite subsequent development of other neurologic manifestations.

SUMMARY

A report is given of an unusual hereditary disorder occurring in three siblings. Their disease began between the ages of three and five, and showed a slowly progressive course with the following features: spastic paresis appearing initially in the legs, gradually extending to the upper extremities, and eventually involving lower cranial nerves; the development of progressive, generalized muscular wasting, probably of neurogenic type, during adolescence; marked skeletal deformities; no impairment of sensation or coordination; normal intelligence.

Special studies, including electromyography, electroencephalography, and muscle biopsy were performed.

REFERENCES

1. Refsum, S.: Heredopathia atactica polyneuritiformis: A familial syndrome not hitherto described, Acta psychiat. et neurol., Supplement 38, 1946.
2. Bickerstaff, E. R.: Hereditary spastic paraplegia, J. Neurol., Neurosurg. & Psychiat. 13: 134, 1950.
3. Landau, W. M., and Gitt, J. J.: Hereditary spastic paraplegia and hereditary ataxia: A family demonstrating a variety of phenotypic manifestations, Arch. Neurol. & Psychiat. 66: 346, 1951.
4. Price, G. E.: Familial lateral sclerosis (spastic paralysis), J. Nerv. & Ment. Dis. 90:51, 1939.
5. Mollaret, P.: L'hérédo-dégénération spino-cérébelleuse, in A. Laffont et F. Durieux: Encyclopédie Médico-chirurgicale, Paris, 1939.
6. Ross, A. T.: Combination of Friedreich's ataxia

and Charcot-Marie-Tooth atrophy in each of two brothers, J. Nerv. & Ment. Dis. 95:680, 1942.
7. Roth, M.: On a possible relationship between hereditary ataxia and peroneal muscular atrophy; with a critical review of the problems of "intermediate forms" in the degenerative disorders of the central nervous system, Brain 71: 416, 1948.
8. Spillane, J. D.: Familial pes cavus and absent tendon-jerks: Its relationship with Friedreich's disease and peroneal muscular atrophy, Brain 63:275, 1940.
9. Murphy, J. P.: Atypical Friedreich's ataxia, report of four cases, with encephalography in one, Yale J. Biol. & Med. 15:603, 1943.
10. Kastan, M.: Different forms of diffuse sclerotic process — Pelizaeus-Merzbacher disease, Strümpell's familial spastic spinal paralysis, leucodystrophy—in one family, J. Nerv. & Ment. Dis. 101:357, 1945.
11. Louis-Bar, D., and Pirot, G.: Sur une paraplégie spasmodique avec dégénérescence maculaire chez deux frères, Ophthalmologica 109: 32, 1945.
12. Philip, R. W.: Primary spastic paralysis and pseudohypertrophic paralysis in different members of the same family, with probable hereditary in both, Brain 8:520, 1886.
13. Fearnsides, E. G.: Familial lateral sclerosis with amyotrophy, Proc. Roy. Soc. Med. 5:144, 1912.
14. Garland, H. G., and Astley, C. E.: Hereditary spastic paraplegia with amyotrophy and pes cavus, J. Neurol., Neurosurg. & Psychiat. 13:130, 1950.
15. Aird, R. B.: Motor neurone diseases, in A. B. Baker: Handbook of Neurology, in press.
16. Van Bogaert, L.: La sclérose latérale amyotrophique de Charcot, Traité de Méd. vol. 16: Maladies du Systéme Nerveux, Part 2, pp. 157-166, Paris, Masson et Cie, 1949.
17. Kreyenberg, G.: Familiäre amyotrophische Lateralsklerose mit hochgradiger Balkenverschmälerung, Ztschr. f. d. ges. Neurol. u. Psychiat. 123:400, 1930.
18. Rütenik, G.: Familiäre amyotrophische Lateralsklerose, Arch. Psychiat. 107:248, 1938.
19. Brown, C. H.: Infantile amyotrophic lateral sclerosis of the family type, J. Nerv. & Ment. Dis. 21:707, 1894.
20. Koerner, D. R.: Amyotrophic lateral sclerosis on Guam: A clinical study and review of the literature, Ann. Int. Med. 37:1204, 1952.
21. Rhein, J. H. W.: Family spastic paralysis, J. Nerv. & Ment. Dis. 44:115, 224, 1916.
22. Bell, J., and Carmichael, E. A.: On hereditary ataxia and spastic paraplegia, Treasury of Human Inheritance, London, Cambridge Univ. Press, 1939, vol. 4, pt. 3.
23. Spiller, W. G.: Fourteen cases of spastic spinal paralysis occurring in one family, Philadelphia M. J. 9:1129, 1902.
24. Refsum, S.: Genetic aspects of neurology, in A. B. Baker, Handbook of Neurology, in press.
25. Shut, J. W.: Hereditary ataxia: Clinical study through six generations, Arch. Neurol. & Psychiat. 63:535, 1950.
26. Wohlfart, G.: Muscular atrophy in diseases of the lower motor neuron: contribution to the anatomy of the motor units, Arch. Neurol. & Psychiat. 61:599, 1944.
27. Schwarz, G. A.: Hereditary (familial) spastic paraplegia, Arch. Neurol. & Psychiat. 68:655, 1952.
28. Van Bogaert, L.: La paraplégie spasmodique familiale du Strümpell-Lorrain, Traité de Méd. vol. 16, Maladies du Système Nerveux, Part 2, pp. 166-169, Paris, Masson et Cie, 1949.
29. Woofter, A. C., and Parks, B. S.: Friedreich's ataxia, Ann. Int. Med. 17:744, 1942.
30. Critchley, M., and Greenfield, J. G.: Olivo-ponto-cerebellar atrophy, Brain 71:343, 1948.
1. Sjögren, T.: Klinische und erbbiologische Untersuchungen über die Heredoataxien, Acta psychiat. et neurol., Supplement 27, 1943.

Another form of clonic spasm is sometimes seen in epileptic fits. Instead of the shock-like clonic spasm, into which the tonic spasm gradually passes, the spasm consists of finer movements, of greater rapidity and less range, and is superadded to, instead of superseding, the tonic spasm. The latter continues, and the strained rigid limbs present this fine rapid movement, almost like a coarse tremor, which maintains the same rapidity instead of becoming less frequent. This form of spasm is often seen in the cases which present flexion of the fingers at all joints and tonic extension of the limbs. Sometimes it occurs in cases with flexor tonic spasm.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Stimulation of the Amygdaloid Nuclear Complex in Unanesthetized Cats

Birger R. Kaada, M.D.,
Per Andersen and Jan Jansen, Jr.

ONLY A FEW experimental studies have dealt with the functional significance of the amygdaloid nuclear complex. Since this structure, situated in the depth of the uncinate region just rostral to the hippocampus, receives a definite projection from the olfactory bulb, it has been thought to serve entirely olfactory functions. However, ablation as well as stimulation of the amygdaloid nuclei have resulted in effects which hardly can be explained entirely on the basis of their presumably purely olfactory function. Thus, bilateral removal of the amygdala in cats has produced a state of anger and increased rage reactions which does not follow removal of the olfactory bulb.[1,2] Bard and Mountcastle[2] postulated that the amygdala acts as a funnel for inhibitory influences on the brain stem mechanism concerned with the integration of anger. Amygdaloid lesions in rats[3] and dogs[4] have, on the other hand, resulted in a decrease of the spontaneous activity of the animal.

Furthermore, it appears that the amygdala receives not only impulses of olfactory origin but also impulses from other sensory systems. In 1936 Gerard, Marshall, and Saul[5] made the incidental observation in cats that the amygdala, as well as the hippocampus and the cortex of the limbic and hippocampal gyri, can be activated also by optic and tactile stimulation. This interesting, but apparently long forgotten, disclosure has recently been confirmed by Robinson and Lennox[6] and Lennox and Madsen[7] who, from the same structures, recorded evoked potentials on acoustic stimulation as well. Moreover, Dell and Olson[8] observed responses from the amygdala – the lateral and central nuclei of this complex only – on stimulation of the vagus nerve in the cat.

Electrical stimulation of the amygdaloid nuclei and the overlying piriform cortex in anesthetized cats and monkeys[9] has elicited a number of complex somatomotor and autonomic responses, such as contraversive movements of the head, eyes, and trunk and tonic movements of the extremities; licking, sniffing, and chewing; inhibition and acceleration of respiratory movements;

From The Anatomical Institute, University of Oslo, Norway.

Read at the Twelfth Scandinavian Neurological Congress, Oslo, September 13, 1952.

inhibition of struggling movements, of tremor and "chloralose-jerks;" facilitation and inhibition of cortically induced movements; salivation, micturition, defecation, and pupillary dilatation. It is of importance to note that several points in the amygdaloid nuclei gave none of these effects in the anesthetized animal. The inhibitory influence on respiratory movements has been confirmed in monkeys.[10] Quite recently Eliasson[11] observed increased gastric contractions on stimulation of these nuclei in anesthetized cats. Finally, stimulation of the amygdala may produce a profound alteration of the spontaneous brain waves in widespread cortical areas, particularly of the frontal lobes.[9]

PROBLEMS

For all the above mentioned stimulation studies, except Dell and Olson's,[8] no attempts have been made to correlate the various responses with the different subdivisions of the amygdala. The latter appears to be a very heterogeneous structure within which a number of nuclei have been distinguished. The fiber connections and phylogenetic development of these nuclei differ. It has been the main purpose of the present experiments to correlate the various somatomotor and autonomic effects which can be elicited by stimulation of the amygdala in cats with the different nuclei of this complex. A similar localization study with respect to the various sensory systems projecting to the amygdala is in progress and will here be only briefly mentioned.

Second, a more detailed study of the somatomotor and autonomic effects has been made possible by stimulating the unanesthetized, freely moving animal through implanted electrodes and by cinematographic analysis of the responses. Further, in view of the results of the ablation studies, it was of particular interest to determine whether any emotional type of reactions could be produced by stimulation, and also whether seizures resembling epileptic automatisms in humans could be precipitated from the amygdala, because such responses have been observed on electrical stimulation of the periamygdaloid cortex in cats[9] and humans.[12]

In a preceding paper[13] the results of similar stimulation of other basal and medial forebrain structures – the hippocampus and the medial prefrontal, limbic, retrosplenial, and hippocampal gyral cortices – have been reported.

ANATOMIC CONSIDERATIONS

Within the amygdaloid complex the following nuclear masses have been distinguished in a number of mammals: [14,15,16] a lateral, a basal (pars medialis parvocellularis and pars lateralis magnocellularis), a medial, a cortical, and a central nucleus; the intercalated masses, the accessory basal nucleus, the nucleus of the lateral olfactory tract, and the anterior amygdaloid area (figures 1 and 2). The latter term designates a rather diffusely outlined area of cells rostral to the amygdaloid nuclear complex proper (figure 2A). These nuclei, or groups of these nuclei, differ from each other with respect to their ontogenetic and phylogenetic development and fiber connections.

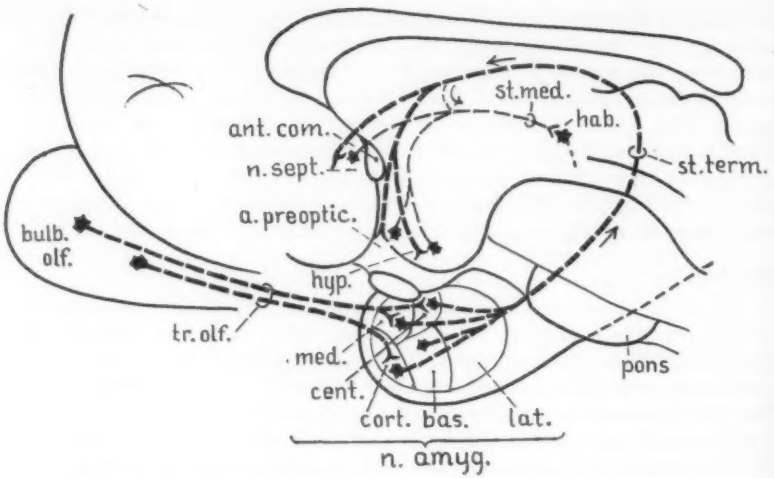


FIG. 1. Diagram of the principal fiber connections of the amygdaloid nuclear complex.

Abbreviations: a. preoptic.—area preoptica; ant. com.—anterior commissure; bas.—nucleus basalis amygdalae; bulb. olf.—bulbus olfactorius; cent.—nucleus centralis amygdalae; cort.—nucleus corticalis amygdalae; hab.—habenula; hyp.—hypothalamus; lat.—nucleus lateralis amygdalae; med.—nucleus medialis amygdalae; n. sept.—nuclei septales; st. med.—stria medullaris; st. term.—stria terminalis; tr. olf.—tractus olfactorius.

Embryologic and comparative anatomic studies. Ontogenetically the amygdaloid nuclear complex appears to develop from a pallial and a subpallial anlage. According to Holmgren,[17] the pallial part in mice gives origin to the lateral and basal nuclei. These nuclei develop from the same anlage as the claustrum and have also been termed the striatal part of the amygdala.[18,19] The subpallial part gives origin to the medial, cortical, and central nuclei. These nuclei – as opposed to the pallial part of the amygdala – were included by Wright[18,19] in his somewhat wider definition of the preoptic region which constitutes " . . . . part of the grey matter in the telencephalon medium as well as the grey matter in the basal part of both hemispheres, and which is interposed between the grey matter of any other region of the hemispheres and the grey matter of the diencephalon." By virtue of contiguity and similarities in their neuronal arrangements, the preoptic region was considered as a morphologic entity. Macchi,[20] on the other hand, reached the conclusion that the entire amygdaloid nuclear complex was of subpallial origin. Recent studies by Källen[21] in humans, however, are in essential agreement with the original findings by Holmgren in mice.

On the basis of comparative anatomic studies, Johnston[14] distinguished a phylogenetically old group of amygdaloid nuclear masses consisting of the medial, cortical, and central nuclei and the nucleus of the lateral olfactory tract, and a phylogenetically younger division comprising the lateral, basal,

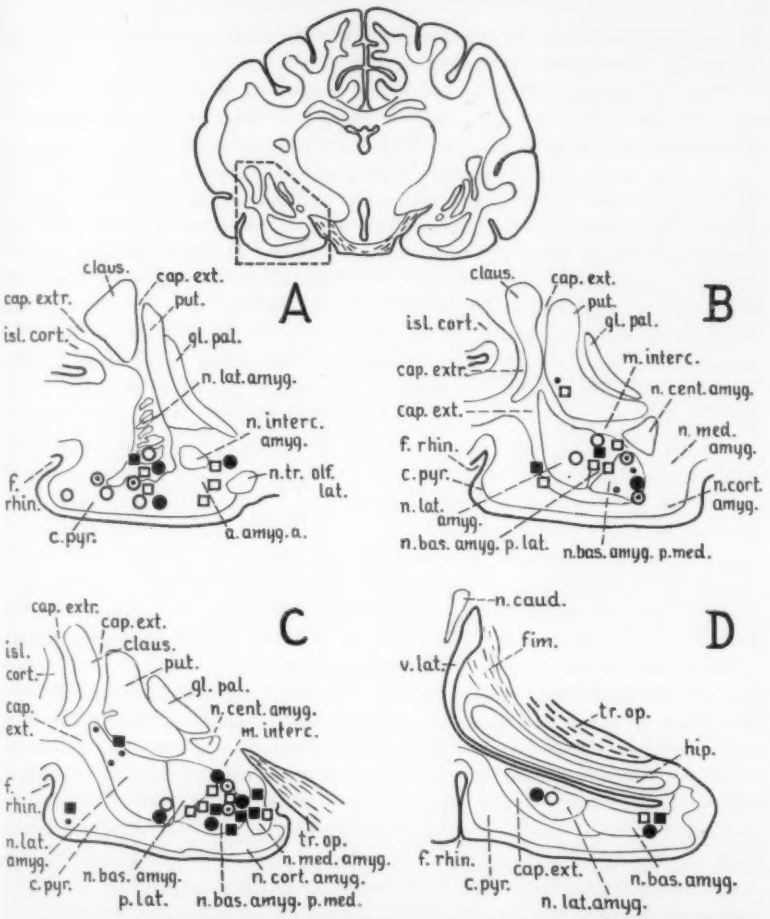


FIG. 2. Frontal sections through the amygdaloid nuclear complex indicating points which produced various somatomotor responses on electrical stimulation. *A* rostral and *D* caudal part of the amygdala. Inset above shows a frontal section through the middle portion of the amygdaloid nuclei, corresponding to section *C*. Filled squares indicate immediate contraversive movements; unfilled squares, movements of the limbs without head turning; filled circles, licking; unfilled circles, sniffing; and dots within circles, chewing.

Abbreviations (for figures 2, 6 and 9—nomenclature according to Fox[15]): a. amyg. a.—area amygdaloidea anterior; cap. ext.—capsula externa; cap. extr.—capsula extrema; c. pyr.—cortex pyriformis; claus.—claustrum; fim.—fimbria; f. rhin.—fissura rhinalis; gl. pal.—globus pallidus; hip.—hippocampus; isl. cort.—island cortex; m. interc.—massa intercalata; n. bas. amyg. p. lat. (p. med.—nucleus basalis amygdalae pars lateralis (pars medialis); n. caud.—nucleus caudatus; n. cent. amyg.—nucleus centralis amygdalae; n. cort. amyg.—nucleus cortalis amygdalae; n. interc. amyg.—nucleus intercalatus amygdalae; n. lat. amyg.—nucleus lateralis amygdalae; n. med. amyg.—nucleus medialis amygdalae; n. tr. olf. lat.—nucleus tractus olfactorii lateralis; put.—putamen; tr. op.—tractus opticus; v. lat.—ventriculus lateralis.

and accessory basal nuclei. The basolateral group is particularly well developed in the primate brain.[22,23] All later workers in the field agree that this part

of the amygdaloid complex occupies a relatively greater portion of the amygdala in the phylogenetic ascent of mammals.

Fiber connections. The main *afferent* projection to the amygdala is from the olfactory bulb which, according to the recent detailed terminal degeneration studies in rabbits by Le Gros Clark and Meyer,[24] distributes its fibers to the nucleus of the lateral olfactory tract and to the medial, cortical, and central nuclei of the amygdaloid complex, in addition to the olfactory tubercle, the piriform cortex, and the bed nuclei of the stria terminalis (figure 1). The olfactory fibers to the amygdala are thus confined to the subpallial or "preoptic"[18,19] part of this structure. It is of interest that the olfactory fibers to the central amygdaloid nucleus and to the bed nucleus of the stria terminalis reach these nuclei bilaterally by way of the anterior commissure, whereas the fibers to the other structures mentioned are distributed homolaterally only, by way of the lateral olfactory tract. In addition to the fibers from the olfactory tract, the amygdaloid nuclei receive afferents from the rostral piriform cortex and, more or less indirectly, from the adjacent temporal polar, postorbital, and anterior insular cortex as shown by physiologic neuronography.[25]

One of the principal *efferent* projections of the amygdaloid nuclear complex is the stria terminalis (figure 1). According to experimental studies by Fox,[26] the stria terminalis in cats contains exclusively efferent fibers with respect to the amygdala. Although there is no full agreement as to the exact origin of the stria fibers within the amygdaloid complex, most workers in the field are of the opinion that the fibers are derived mainly from the medial, cortical, and central nuclei – "the medial amygdaloid group" of Fox[15] – and probably from the basal nucleus and the nucleus of the lateral olfactory tract.[26] The fibers of the stria terminalis are distributed mainly to the septal, preoptic, and hypothalamic areas. Some fibers possibly also reach the habenula by way of the stria medullaris, (for contradictory results, refer to Adey and Meyer[27]). According to the latter authors, the stria terminalis fibers in the monkey terminate mainly in the ventromedial and periventricular arcuate nuclei of the hypothalamus of the homolateral hemisphere. Some fibers also reach the corresponding nuclei of the opposite hemisphere. While the amygdaloseptal fibers of the stria terminalis connect the septum and the amygdala above the internal capsule, the diagonal band does likewise below the internal capsule.

The amygdaloid nuclei further contribute fibers to the anterior commissure which interconnect the olfactory bulbs, the anterior olfactory nuclei, the olfactory tubercles, the nuclei of the lateral olfactory tract, the piriform cortices, the bed nuclei of the stria terminalis, and part of the neopallial cortex of the temporal lobe of the two hemispheres.[28,29] There appears to be no agreement concerning the exact origin of the commissural fibers from the amygdaloid nuclei. Whereas most students of normal material state that the fibers are derived from the lateral and partly from the basal nuclei, Brodal[29]

found retrograde changes in the medial and cortical amygdaloid nuclei, the anterior amygdaloid area, and to some extent in the medial small-celled part of the basal nucleus on sectioning the anterior commissure in rats. To what extent the fibers of the anterior commissure are truly commissural in the sense that they interconnect homologous areas of the two hemispheres can only be determined in more experimental work.

In summary it may be stated that on the basis of embryologic and phylogenetic studies and on the basis of known afferent and efferent fiber connections, the amygdala as a whole may be divided into two portions: 1) a phylogenetically old, anteromedial division consisting of the medial, cortical, and central nuclei, the nucleus of the lateral olfactory tract and of the anterior amygdaloid area, and which receives a definite projection from the olfactory bulb and projects to the septal, preoptic, and hypothalamic areas; and 2) a phylogenetically younger basolateral division which appears to have no direct connection with the fibers from the olfactory bulb and which, with the possible exception of the basal nucleus, probably does not project its fibers to the stria terminalis. Whether, in addition to the anteromedial division, the basolateral division also contributes fibers to the anterior commissure needs further investigation. More information on the connections of the basal and lateral nuclei with other parts of the brain are needed.

The experiments to be reported below indicate the existence of functional differences as well between the anteromedial and lateral divisions of the amygdaloid complex, whereas the basal nucleus appears to take an intermediate position between the two.

MATERIAL AND METHODS

A total of 33 electrodes were implanted in the amygdaloid region in 13 adult cats. In addition, 13 electrodes were placed in the adjacent cortex of the anterior end of the hippocampal gyrus. The procedure employed was the same as that described previously.[13] Briefly, on the first day the cats were anesthetized with a mixture of Nembutal and chloralose, and bipolar needle electrodes insulated except for the tips were implanted. While the animal was still under anesthesia the effect of stimulation on respiratory movements was recorded kymographically. Square wave pulses at a frequency around 40 per sec., a pulse duration of 10 msec., and intensities of 2 to 6 volts for five to 30 seconds were commonly employed. The next day the somatomotor, autonomic, and behavior responses to stimulation of the conscious and freely moving cats were studied and recorded on 16 mm. Kodachrome film. In a terminal experiment the animals were again anesthetized in order to study the effects of stimulation of the same points in the amygdala on the electrocorticogram and for recording potentials evoked on acoustic and tactile stimulation. The sites of stimulation were identified histologically.

RESULTS

Somatomotor responses.

Immediate contraversive movements. The most striking and frequent response to amygdala stimulation in unanesthetized cats was an immediate and strong turning of the head, eyes, and upper part of the body, invariably to

the opposite side (figure 3). This response lasted as long as the stimulus was on, from a few seconds to one-half minute, and at the end of stimulation the original position was immediately resumed. The turning was usually associated with a backward-upward movement of the head and tonic extension of the ipsilateral or both forelimbs, resulting in a characteristic spiral movement of the head and upper part of the body. The rotation of the head frequently reached an extreme degree; it could turn 180 degrees so that the animal was looking backwards at its own tail; or the rotation could continue further until the animal lost its equilibrium and fell on its side. In a few experiments the lower part of the trunk also participated more or less in the contralateral turning, resulting in rotation of the entire animal around its longitudinal axis. By increasing the stimulus strength there were sometimes three or four complete turns in rapid succession.

From some points isolated tonic movements of one or more extremities without any clear head turning were produced. The most common response was a synergetic flexion and retraction of the contralateral hindleg which was often associated with a flexion of the contralateral foreleg and extension of the ipsilateral legs. Occasionally there was a strong extension of all four legs with the head, trunk, and tail in opisthotonus.

These tonic movements of the head, trunk, and limbs were obtained by stimulation of points located almost exclusively in the medial and anterior portions of the amygdaloid complex (nucleus medialis, nucleus basalis pars medialis, the anterior amygdaloid area [figure 2, squares]). A few points were located in the periamygdaloid cortex, one in the putamen and one on the border between putamen and the amygdaloid nuclei. No immediate head turning was produced by stimulation of several points in the nucleus lateralis.

Clonic movements. Frequently twitchings of the homolateral side of the mouth, the eyes, or the face were seen. More rarely, similar jerking movements might also involve the contralateral limbs. These clonic movements usually occured at low stimulus strengths, and rarely proceeded into generalized convulsions.

Licking, sniffing, and chewing. These effects were similarly most frequently obtained from the medial and anterior group of amygdaloid nuclei (figure 2, circles). Points yielding licking and sniffing were found also in the nucleus lateralis and nucleus basalis pars lateralis, whereas chewing movements were produced by stimulation of points in the anteromedial group of nuclei only. Licking and chewing, as well as licking and sniffing, were frequently obtained from the same point. The animal was either licking and sniffing along the floor (figure 4A), or it turned its head slowly with searching movements to the opposite side and started to lick itself and to sniff around its own fur (figure 4B), frequently about the opposite groin (figure 5). The latter effect was most prominent when the lateral portion of the amygdala was stimulated. The eyes might for a moment fix on a certain part of the body before the licking and sniffing started, sometimes quite vigorously. Lip-licking was

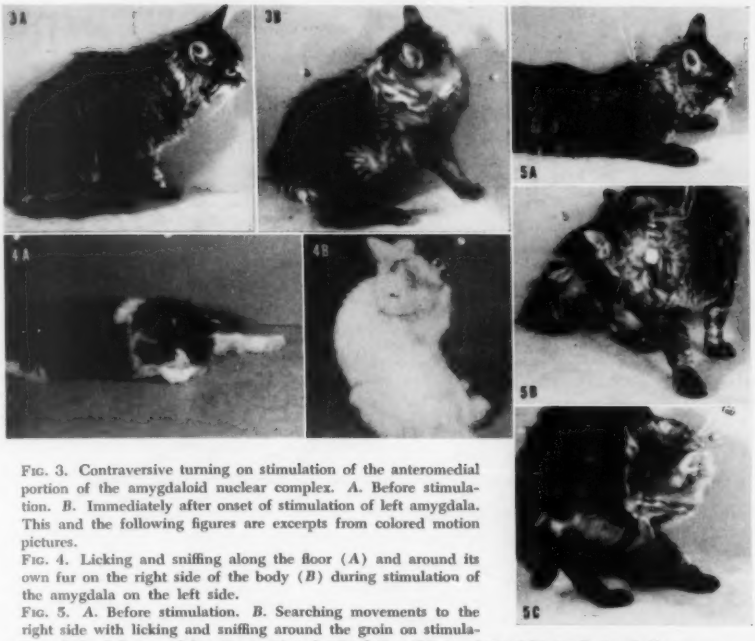


FIG. 3. Contraversive turning on stimulation of the anteromedial portion of the amygdaloid nuclear complex. *A.* Before stimulation. *B.* Immediately after onset of stimulation of left amygdala. This and the following figures are excerpts from colored motion pictures.

FIG. 4. Licking and sniffing along the floor (*A*) and around its own fur on the right side of the body (*B*) during stimulation of the amygdala on the left side.

FIG. 5. *A.* Before stimulation. *B.* Searching movements to the right side with licking and sniffing around the groin on stimulation of the left amygdala. On continued stimulation this turning might result in circling movements performed at considerable speed to the side opposite to that being stimulated (*C*).

most commonly seen as a result of stimulation of the medial and anterior nuclei.

A given type of response could be repeated on numerous trials in a rather stereotyped fashion, characteristic for each point. Whether the animal licked its own fur or along the floor was not dependent on its original position or occupation.

The licking and sniffing started within a few seconds after the onset of stimulation and continued as long as the stimulus was on, whereas the chewing movements usually occurred after a latency of some 10 to 15 seconds. In some animals a few licking movements about the lips occurred as a rebound effect.

Inhibition of somatomotor activities. Stimulation of points situated mainly in the anteromedial group of amygdaloid nuclei produced an immediate inhibition of respiratory movements (figure 6). The chest usually assumed an expiratory position during the period of apnea (figure 7). The respiratory movements could not ordinarily be held in abeyance for more than 40 to 60 seconds despite continuous stimulation, after which period respiratory "escape" occurred. In a few animals, however, respiration ceased for a considerable

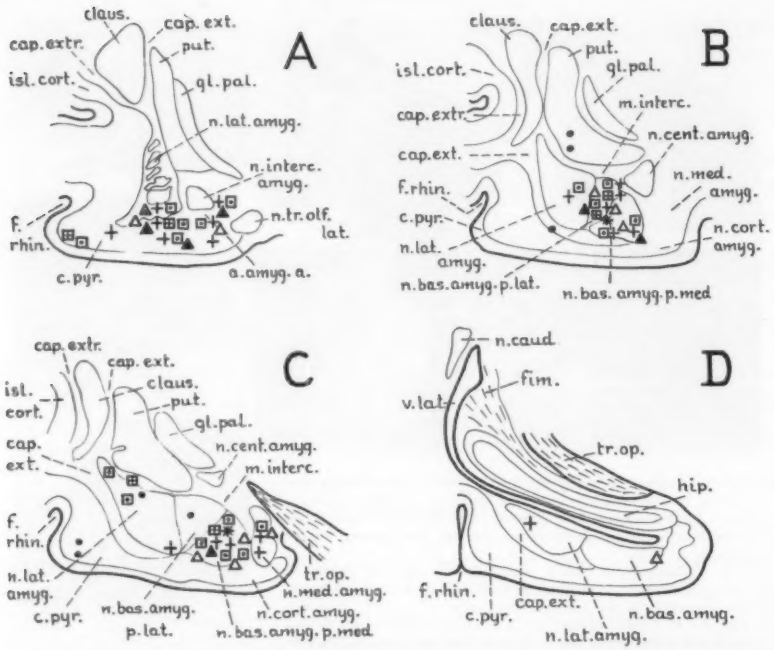


FIG. 6. Frontal sections through the amygdaloid nuclear complex indicating points which produced various autonomic and respiratory responses on electrical stimulation. Abbreviations as in figure 2. Cross indicates inhibition (in expiration) of respiratory movements; cross within square, acceleration of respiratory movements; dot within square, pupillary dilatation; star, pilo-erection; filled triangle, salivation; unfilled triangle, micturition; dot within triangle, defecation.

period after interruption of the stimulation, which necessitated artificial respiration in order to stimulate the animal to spontaneous respiration. Occasionally respiration ceased during inspiration, usually associated with tonic movements of the trunk and limbs, and in some animals acceleration of breathing associated with a slight diminishing of the excursions was noted, particularly when the animal was awake.

Stimulation of points which yielded inhibition of respiratory movements in expiration also produced inhibition of other spontaneous somatomotor activities such as struggling and shivering (figure 7) and of "chloralose jerks," thus confirming previous observations by one of us.[9] The muscular tone, as judged by the resistance to passive motion and by palpation of the muscle bellies, was similarly reduced on stimulation of the same amygdaloid points.

AUTONOMIC RESPONSES

A number of autonomic effects resulted from amygdaloid stimulation in unanesthetized as well as in anesthetized cats. The stimulus threshold for these responses was generally about the same as that for the somatomotor

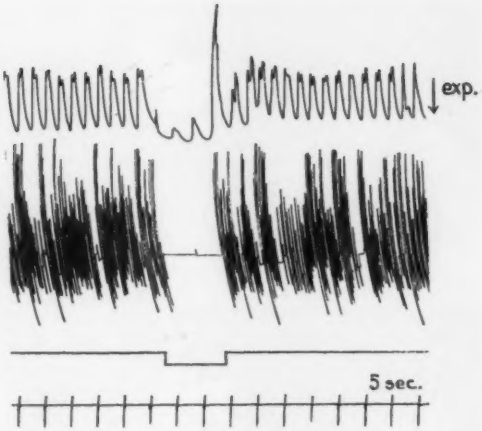


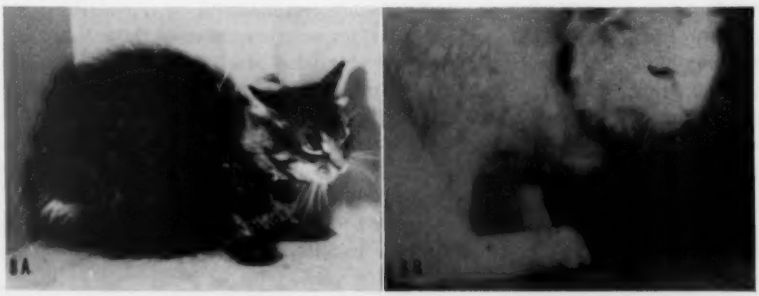
FIG. 7. Inhibition of respiratory movements in expiration (upper tracing) and inhibition of spontaneous shivering recorded from one hind-limb (second tracing) by stimulating the anteromedial division of the amygdaloid nuclear complex.

effects. Various autonomic responses could be obtained from the same point.

Pupillary dilatation. The size of the pupils was observed in all experiments. Bilateral dilatation occurred on stimulation of 17 of the 33 electrode sites (figure 6). The responsive points were located in all divisions of the amygdaloid complex, but there appeared to be a difference in the latency and degree of the effects obtained from the anteromedial portion and from the lateral part, respectively. From the former the dilatation was usually more immediate and stronger than from the latter region, where it occurred more slowly and reached a maximum after several seconds. This slow response was usually part of the "attention" response to be described below.

Salivation. Abundant secretion of a thick and mucous saliva (figure 8B) was produced from seven electrode sites, six of which were located in the anteromedial nuclear group and the last one in the medial part of the lateral nucleus, on the border toward the basal nucleus (figure 6). Salivation was

FIG. 8. Pilo-erection (*A*) and salivation (*B*) caused by stimulating the medial part of basal amygdaloid nucleus.



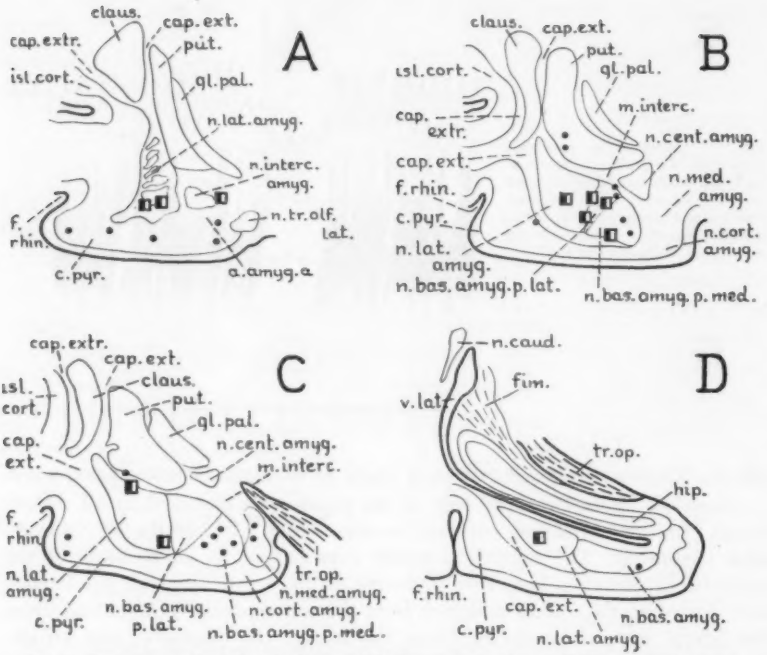
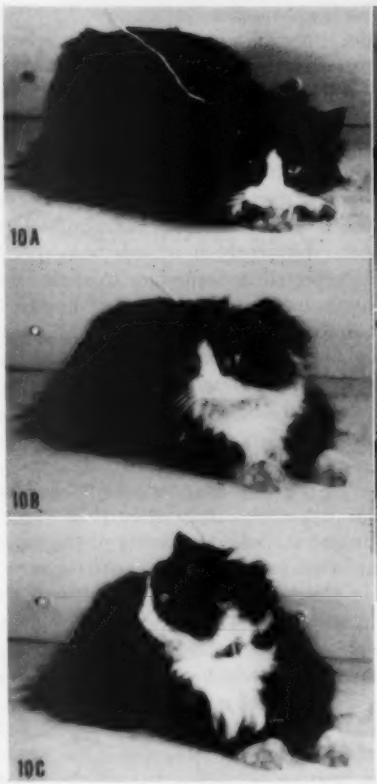


FIG. 9. Transverse sections through the amygdala demonstrating sites (half-filled squares), stimulation of which elicited behavior responses ("attention," searching, and glancing movements to the contralateral side) similar to those produced from the hippocampus, fornix, and medial cortical areas.[13] Dots: no such responses. Abbreviations as in figure 2.

frequently, but not always, associated with licking, swallowing, or chewing movements.

Micturition and defecation. Micturition was recorded on stimulation through 10 of the 33 implanted electrodes, all situated in the anteromedial group of nuclei and in the basal nucleus (figure 6). It usually occurred within the first few seconds after onset of stimulation and could be repeated several times in succession or on different occasions on stimulation of the same point. In one animal the urinary bladder was visualized after a wide laparotomy in a terminal experiment. In this case vigorous contractions of the bladder were seen to occur repeatedly coincident with stimulation of an amygdaloid point which had produced micturition, indicating that the latter effect was not due to contraction of the abdominal wall. Defecation resulted from stimulation of one electrode only. This was placed in the anterior amygdaloid region.

Pilo-erection. Pilo-erection (figure 8A) was seen in two cats on stimulation of points in the medial part of the basal amygdaloid nucleus (figure 6B and C).



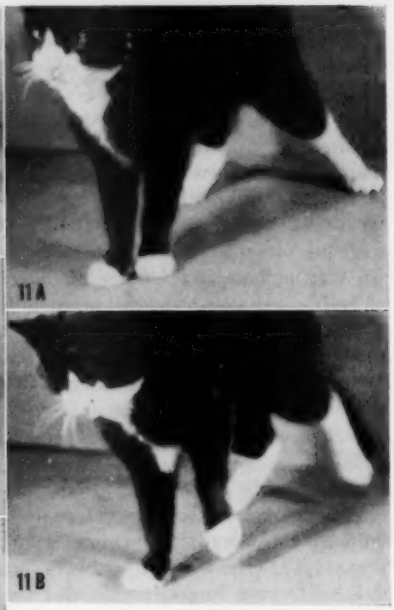


FIG. 10. *A.* Before stimulation. *B* and *C.* Searching to the right side caused by stimulating the left lateral amygdaloid nucleus.

FIG. 11. *A.* Before stimulation. *B.* Rhythmic and gentle stepping of left foreleg and hindleg resulting from stimulation of the lateral part of basal amygdaloid nucleus on the contralateral side.

BEHAVIOR CHANGES

Stimulation of points located mainly in the lateral nucleus and the lateral portion of the basal nucleus of the amygdaloid complex (figure 9) produced changes in behavior almost identical to those obtained by excitation of the hippocampus and the medial prefrontal, limbic, retrosplenial, and hippocampal gyral cortices as described in a preceding paper.[13] The response consisted in cessation of all spontaneous preoccupation, changes of the facial expression to one of "attention" or vigilance associated with some surprise and bewilderment (figure 10). The animal raised its head, pricked its ears, and performed quick glancing or searching movements always to one side, contralateral to that stimulated. The pupils dilated slowly. This searching was not directed towards external stimuli but apparently towards some kind of psychic experience or something imaginary in the environment. When the stimulus strength was increased, several cats showed signs of fright and

anger or fury, the latter of a defensive rather than of an aggressive character.

Besides this searching and orientation directed towards the surroundings and resembling reactions to visual, acoustic or olfactory sensations, stimulation of other points in the lateral nucleus and the lateral part of the basal amygdaloid nucleus produced reactions in which the cat fixed its attention towards a certain area of the contralateral side of its own body. It appeared as if the animal experienced some kind of bodily sensation. After having fixed this area of the body with its eyes for a moment, it started to lick and sniff around on its fur on the opposite side, either on its back or around the groin. This might result in regular circling movements, frequently at considerable speed.

Another type of response, similarly interpreted as secondary to some kind of bodily sensation, was produced in three animals. Stimulation of points in the basolateral portion of the amygdaloid complex resulted in rhythmic stepping movements of the opposite foreleg (figure 11) or, more rarely, of the opposite hindleg. The paw in each sequence barely touched the floor and was rapidly withdrawn, as if the animal experienced a burning sensation.

COMMENT

The present study confirms and extends previous observations by Kaada[9] that complex somatomotor and autonomic responses can be elicited by stimulation of the amygdaloid nuclear complex and the adjacent cortex of the uncal region. The experiments further indicate that various portions of the amygdala subserve different functions. From a physiologic point of view it appears that two different portions can be distinguished within the amygdaloid complex: 1) an anteromedial division which responds with autonomic and immediate somatomotor effects to stimulation, and which appears to coincide approximately with the phylogenetically old group of nuclear masses receiving projections from the olfactory bulb and projecting to the septal, preoptic, and hypothalamic areas (the subpallial part of the amygdala); and 2) a lateral division which on stimulation yields the various behavior changes described above, and which appears to coincide with the phylogenetically younger group of amygdaloid nuclei (of pallial origin).

Physiologically the basal nucleus, belonging to the pallial part, appears to take an intermediate position from which both types of responses can be produced by stimulation. This may possibly be due to the fact that the basal nucleus is situated between the anteromedial group of nuclei and the lateral nucleus. The possibility of stimulating the neighboring cells of these nuclei cannot be excluded in spite of the fact that control experiments showed that the area yielding a given response was rather critical; moving the electrode one or two millimeters in either direction frequently made the response disappear completely. A second explanation may be that fibers from the anteromedial group of nuclei or the lateral nucleus pass through this intermediate zone occupied by the basal nucleus. Finally, there may actually exist functional differences between various parts of this nucleus. A distinction should perhaps be made also physiologically between the lateral large-celled part

and the medial small-celled part of the basal nucleus, the former giving predominantly reactions similar to the lateral nucleus and the latter approaching more the anteromedial group in its effects by stimulation. It should also be recalled that from a developmental point of view the basal nucleus possesses affinities with the lateral nucleus, both together constituting the pallial part of the amygdala, whereas, when considering the fiber connections, the basal nucleus – or perhaps only part of this nucleus – should be placed with the anteromedial group, since it sends efferent fibers via the stria terminalis.

The production of behavior responses from the basolateral portion of the amygdala, almost indistinguishable from those which can be elicited from the hippocampus and parts of the cortex of the medial prefrontal, limbic, and hippocampal gyral regions,[13] indicates structural and functional relationships between all these areas. A further study of this relationship and of the nervous structures involved is in progress.

It is of further importance to establish whether the amygdaloid areas from which the searching response can be elicited coincide with the areas which receive visual, acoustic, and somesthetic impulses. Preliminary experiments suggest that this might be so, but a more detailed study is necessary before any definite statements can be made regarding this point. This is of particular interest in view of the fact that the hippocampus and the cortex of the limbic and hippocampal gyri can also be activated by such afferent stimulation. It appears likely that the searching response consisting of quick glancing movements to the contralateral side may be reactions to visual or acoustic sensations ("hallucinations") produced by excitation of these structures. Similarly the licking of the contralateral side of the body and the rhythmic gentle stepping movements of the contralateral legs on stimulation of the basolateral portion of the amygdala are possibly caused by the evocation of some kind of somesthetic impressions. On the other hand, licking and sniffing in response to stimulation of the anteromedial group which receives fibers directly from the olfactory bulb may be related to the sense of smell.

Apposite to these considerations, it is also of importance in future experiments to determine whether the gastrointestinal responses to amygdaloid stimulation[11] are restricted to the areas from which Dell and Olson[8] have recorded evoked potentials in response to afferent vagal stimulation, namely, the lateral and central amygdaloid nuclei.

Finally, the implications of the results presented for certain types of *temporal lobe seizures* need consideration. It has been generally established that in the majority of cases of epileptic automatisms the electroencephalographic disturbances are found within the anterior and basal temporal regions, that is, in close relation to the structures dealt with in the present study. According to Jasper, Pertuisset, and Flanigin,[12] about one-half of all seizures which seem to be of focal cortical origin arise within the temporal lobe.

The clinical picture of epilepsy originating from the anterior temporal region is rather complex, including a variety of somatomotor (tonic or contraversive movements; chewing, swallowing, sucking, licking, or smacking of

the lips; overbreathing, respiratory arrest), autonomic (pallor, flushing, palpitation, salivation, borborygmus), special sensory (somatosensory, olfactory, taste, epigastric, or precordial sensation) and psychic manifestations.

Epileptic seizures in which masticatory movements occur have been specially studied by Penfield and Kristiansen[30] and by Magnus, Penfield, and Jasper.[31] These authors emphasized that mastication in seizures is not a sign comparable to the motor phenomena of the classical Jacksonian attack, but that it really constitutes an automatism and that it, like other automatisms, is associated with a disturbance of consciousness. Since epileptic seizures associated with regular chewing movements could be elicited in cats by electrical stimulation of the amygdala and of the overlying piriform cortex in the absence of the precentral motor cortex, Kaada[9] suggested that mastication in epileptic automatism may arise from these basal areas of the forebrain. Similar conclusions have been reached by Magnus, Penfield, and Jasper[31] who found that the epileptogenic foci in patients with masticatory seizures were most frequently situated in an area extending from the insula to the tip of the temporal lobe. They may also be localized on the lateral surface of the temporal lobe, and, exceptionally, in the lower central and the lateral frontal regions. These authors suggested that a subcortical mechanism must be activated to obtain mastication from the temporal region and that the amygdaloid nuclei with its efferent projections to the diencephalic and mesencephalic levels would be the most likely subcortical structure involved. It is pertinent to note that the long latency of usually 10 to 15 seconds, which characterizes the masticatory responses to stimulation of the amygdala and the overlying cortex, is commonly also encountered in epileptic automatism with mastication.

Contraversive turning of the head and usually also of the eyes is a frequent sign in temporal lobe seizures. This turning was considered by Magnus, Penfield, and Jasper[31] to be of special diagnostic importance as it is often the only clinical manifestation to indicate the side of the lesion. In their series, turning to the ipsilateral side was only seen once and in that case it was preceded by brief but definite turning to the contralateral side. In our experiments the turning produced by stimulation of the amygdala and the piriform cortex was, without exception, toward the contralateral side. It appears to us that turning in temporal lobe seizures is due to involvement of the amygdala and adjacent cortex in the epileptic discharge. The same applies to the general rigidity and tonic extension of the contralateral or both limbs, rotating movements, twitching of the contralateral side of the face, and slow jerking movements of the limbs frequently seen in temporal lobe seizures.

The various autonomic and respiratory phenomena in temporal lobe seizures can all be produced by stimulation of the amygdala. Such responses may also be obtained on stimulation of the temporal pole and the adjacent anterior insular cortex in monkeys[9,32,33,34] and in man.[35,36,37] Since the temporal polar cortex appears to project to the amygdaloid nuclei,[25] it is likely that at least some of the autonomic and respiratory effects obtained from adjacent cortical areas are mediated through the amygdala.

Regarding the various psychic manifestations of temporal lobe seizures, stimulation experiments in animals obviously cannot give much reliable information. It should be emphasized, however, that the quick and anxious glancing movements described above bear a striking resemblance to the behavior changes seen in some patients with epileptic automatism. The fear and the frightening thoughts often associated with temporal automatism[30,31] may be caused by interference with the same temporal structures from which reactions expressing fear, anger, and fright have been produced in our cats.[13]

Addendum: Gastaut and associates[38,39,40] have quite recently confirmed the original observation by one of us[9] that a number of somatomotor and visceral effects can be elicited by stimulating the amygdaloid nuclei. They have also produced various behavior responses similar to those described here.

SUMMARY

1. Electrical stimulation of the amygdaloid nuclear complex in unanesthetized cats has elicited complex somatomotor and visceromotor effects: contraversive movements, tonic and clonic movements of the extremities, licking, sniffing, chewing, and inhibition of respiratory and other spontaneous somatomotor activities; pupillo-dilation, salivation, micturition, defecation, and pilo-erection. These responses were obtained mainly from the phylogenetically old anteromedial division of the amygdaloid nuclei which receives fibers from the olfactory bulb and which projects to the septal, preoptic, and hypothalamic areas.

2. Stimulation of the phylogenetically younger basolateral division, which appears to have no direct connections with fibers from the olfactory bulb and whose efferent projections are unknown, produced behavior changes very similar to those obtained by stimulating the hippocampus and the medial prefrontal, limbic, retrosplenial, and hippocampal gyral cortices, indicating functional relationships between all these structures. This response consisted of searching movements to the contralateral side associated with bewilderment and anxiety, and sometimes with fear, anger, and fury.

3. The results are discussed in relation to temporal lobe seizures. It is believed that the amygdala plays an important role in certain types of epileptic automatisms.

Nembutal was kindly supplied by Abbott Laboratories Ltd., and chloralose by E. Merck, Darmstadt.

REFERENCES

1. Spiegel, E. A.; Miller, H. R., and Oppenheimer, M. J.: Forebrain and rage reactions, J. Neurophysiol. 3:538, 1940.
2. Bard, P., and Mountcastle, V. B.: Some forebrain mechanisms involved in expression of rage with special reference to suppression of angry behavior, A. Res. Nerv. & Ment. Dis., Proc. 27:362, 1948.
3. Anand, B. K., and Brobeck, J. R.: Food intake and spontaneous activity of rats with lesions in the amygdaloid nuclei, J. Neurophysiol. 15:421, 1952.
4. Rosvold, H. E.; Fuller, J. L., and Pribram, K. H.: (Quoted by Fulton, J. F.: Frontal Lobotomy and Affective Behavior, New York, W. W. Norton & Co., 1951, p. 80 et seq.)
5. Gerard, R. W.; Marshall, W. H., and Saul, L. J.: Electrical activity of the cat's brain, Arch. Neurol. & Psychiat. 36:675, 1936.
6. Robinson, F., and Lennox, M. A.: Concern-

ing sensory mechanisms in hippocampus, cingulate gyrus, and cerebellum of the cat, Federation Proc. 10:110, 1951.
7. Lennox, M., and Madsen, A.: Sensory representation in olfactory brain, Acta physiol. scandinav. 23 (suppl. 89): 53, 1951.
8. Dell, P., and Olson, R.: Projections "secondaires" mésencéphaliques, diencéphaliques et amygdaliennes des afférences viscérales vagales, Compt. rend. Soc. biol. 145:1088, 1951.
9. Kaada, B. R.: Somatomotor, autonomic and electrocorticographic responses to electrical stimulation of "rhinencephalic" and other structures in primates, cat and dog, Acta physiol. scandinav. 24 (suppl. 83): 285, 1951.
10. Wall, P. D., and Davis, G. D.: Effects of electrical stimulation of temporal lobe in the rhesus monkey, Federation Proc. 9:132, 1950.
11. Eliasson, S.: Cerebral influence on gastric motility in the cat, Acta physiol. scandinav. 26 (suppl. 95): 70, 1952.
12. Jasper, H.; Pertuisset, B., and Flanigin, H.: EEG and cortical electrograms in patients with temporal lobe seizures, Arch. Neurol. & Psychiat. 65:272, 1951.
13. Kaada, B. R.; Jansen, J., Jr., and Andersen, P.: Stimulation of the hippocampus and medial cortical areas in unanesthetized cats, Neurology, 3:844, 1953.
14. Johnston, J. B.: Further contributions to the study of the evolution of the forebrain, J. Comp. Neurol. 35:337, 1923.
15. Fox, C. A.: Certain basal telencephalic centers in the cat, J. Comp. Neurol. 72:1, 1940.
16. Brodal, A.: The amygdaloid nucleus in the rat, J. Comp. Neurol. 87:1, 1947.
17. Holmgren, N.: Points of view concerning forebrain morphology in higher vertebrates, Acta zoolog. 6:415, 1925.
18. Wright, M. K.: The definition of the preoptic region in subprimate mammalian brains, with special reference to the elephant shrew, South African J. M. Sc. 15:15, 1950.
19. Wright, M. K.: The fibre connections of the preoptic region in subprimates with special emphasis on the medial forebrain bundle, South African J. M. Sc. 15:33, 1950.
20. Macchi, G.: The ontogenetic development of the olfactory telencephalon in man, J. Comp. Neurol. 95:204, 1951.
21. Kallen, B.: The nuclear development in the mammalian forebrain with special regard to the subpallium, Lunds Universitets Aarsskrift. Kungl. Fysiografiska Sällskapets Handlingar, Sweden, 61:1, 1951.
22. Crosby, E. C., and Humphrey, T.: Studies of the vertebrate telencephalon: II. the nuclear pattern of the anterior olfactory nucleus, tuberculum olfactorium and the amygdaloid complex in adult man, J. Comp. Neurol. 74:309, 1941.
23. Lauer, E. W.: Nuclear pattern and fiber connections of certain basal telencephalic centers in macaque, J. Comp. Neurol. 82:215, 1945.
24. Clark, W. E. LeGros, and Meyer, M.: The terminal connexions of the olfactory tract in the rabbit, Brain 70:304, 1947.
25. Pribram, K. H.; Lennox, M. A., and Dunsmore, R. H.: Some connections of the orbitofronto-temporal, limbic and hippocampal areas of *Macaca mulatta*, J. Neurophysiol. 13:127, 1950.
26. Fox, C. A.: The stria terminalis, longitudinal association bundle, and precommissural fibers in the cat, J. Comp. Neurol. 79:277, 1943.
27. Adey, W. R., and Meyer, M.: Hippocampal and hypothalamic connexions of the temporal lobe in the monkey, Brain 75:358, 1952.
28. Fox, C. A., and Schmitz, J. T.: A Marchi study of the distribution of the anterior commissure in the cat, J. Comp. Neurol. 79:297, 1943.
29. Brodal, A.: The origin of the fibers of the anterior commissure in the rat: Experimental studies, J. Comp. Neurol. 88:157, 1948.
30. Penfield, W., and Kristiansen, K.: Epileptic Seizure Patterns: A study of the Localizing Value of Initial Phenomena in Focal Cortical Seizures, Springfield, Illinois, Charles C Thomas, 1951.
31. Magnus, O.; Penfield, W., and Jasper, H.: Mastication and consciousness in epileptic seizures, Acta psychiat. et neurol. scandinav. 27: 91, 1952.
32. Kaada, B. R.; Pribram, K. H., and Epstein, J. A.: Respiratory and vascular responses in monkeys from temporal pole, insula, orbital surface and cingulate gyrus: A preliminary report, J. Neurophysiol. 12:347, 1949.
33. Poirer, L. J.: Anatomical and experimental studies on the temporal pole of the macaque, J. Comp. Neurol. 96:209, 1952.
34. Wall, P. D., and Davis, G. D.: Three cerebral cortical systems affecting autonomic function, J. Neurophysiol. 14:507, 1951.
35. Chapman, W. P.; Livingston, K. E., and Poppen, J. L.: Effect upon blood pressure of electrical stimulation of tips of temporal lobes in man, J. Neurophysiol. 13:65, 1950.
36. Liberson, W. T.; Scoville, W. B., and Dunsmore, R. H.: Stimulation studies of the prefrontal lobe and uncus in man, Electroencephalog. & Clin. Neurophysiol. 3:1, 1951.
37. Kaada, B. R., and Jasper, H.: Respiratory responses to stimulation of temporal pole, insula, and hippocampal and limbic gyri in man, Arch. Neurol. & Psychiat. 68:609, 1952.
38. Gastaut, R.; Vigouroux, R.; Corriol., J., and Badier, M.: Effects de la stimulation électrique (par électrodes à demeure) du complexe amygdalien chez le chat non narcosé, J. physiol. Paris 43:740, 1951.
39. Vigouroux, R.; Gastaut, H., and Badier, M.: Les formes expérimentales de l'épilepsie. Provocation des principales manifestations cliniques de l'épilepsie dite temporale par stimulation des structures rhinencéphaliques chez le chat non anesthésié, Rev. neurol. 85:505, 1951.
40. Gastaut, H.; Naquet, R.; Vigouroux, R., and Corriol, J.: Provocation de comportements émotionnels divers par stimulation rhinencéphalique chez le chat avec électrodes a demeure, Rev. neurol. 86:319, 1952.

Cerebral Angiography in Carotid Cavernous Communications

Thomas C. Parsons, M.D., Emanuel J. Guller, M.D., Harold G. Wolff, M.D. and Howard S. Dunbar, M.D.

ALTHOUGH cerebral angiography has become a well established diagnostic technic in the study of intracranial vascular lesions, its use as a method for studying the pathophysiology of the cerebral circulation is, as yet, in its exploratory phase. This observation is especially pertinent in cases of caroticocavernous fistulae, of which Lima[1] reported opportunity for angiographic study in only two instances. Mense,[2] in his review of the subject, collected 12 cases from the literature, including three of his own, in which cerebral angiograms were performed. With the increasing utilization of this technic, radiologists and neurologists alike have secured valuable information regarding channels of altered circulation, and the neurosurgeon has been guided in the appropriate operative management of these cases.

Caroticocavernous fistulae are frequently posttraumatic, although about 25 per cent of the cases appear to be spontaneous with no specific traumatic antecedent.[3] The latter are probably due to rupture of an aneurysm of the internal carotid artery in its course through the cavernous sinus.

Traumatic caroticocavernous fistulae are usually secondary to basal skull fractures consequent to the application of force either to the anterior or lateral aspects of the head. The fracture usually follows lines of structural weakness toward the center of the cranial bases, converging on the body of the sphenoid bone and frequently extending across the base of the skull to the opposite side, producing lacerations of one or both carotid arteries within the cavernous sinus as illustrated by Rawling.[4]

In the case reported here, the relationship of trauma is both recent and distinct. The case is of further interest in that it presents an example of spontaneous occlusion following angiography.

CASE PRESENTATION

A 38 year old white woman, a schizophrenic for many years, was admitted to the Montrose Veterans Administration Hospital March 22, 1951. Admission examinations were within normal limits with the exception of the evidence of mental illness, briefly described

From the neurology, radiology, and neurosurgery services, Veterans Administration Hospital, Montrose, New York.

FIG. 1. Upper arrow points to the carotid-cavernous aneurysm and the large venous trunk formed by the junction of the superior and inferior ophthalmic veins in their course from the orbit. The lower arrow points to the facial vein in its course toward the angle of the mouth.
FIG. 2. Repeat left angiogram four months later—arteriovenous aneurysm no longer apparent.

as chronic schizophrenic reaction with predominance of hebephrenic and paranoid features.

As a result of ineffectual control of the mental symptomatology by electroconvulsive therapy, hydrotherapy, and other measures, a bilateral prefrontal lobotomy was performed on June 19, 1952. The procedure was attended by no complications, and an uneventful convalescence took place.

On July 28, 1952, the patient had two generalized grand mal type seizures, and as a result of the second seizure she fell striking the occiput. Following the injury she was stuporous, restless, vomited freely, and dark venous blood drained from the right ear. There was no nuchal rigidity or other neurologic changes, except slight internal strabismus. A skull roentgenogram disclosed no fracture. A spinal puncture performed within one hour after the injury showed pressure of 130 mm. of water and the centrifuged fluid was clear and colorless. The patient complained of dull headache, but within five days following the injury this symptom had subsided, consciousness returned to normal, and the mental picture definitely improved.

On August 8, 1952, the patient began to complain again of headaches and became apathetic and listless. Several days later her left eye became swollen and injected. The ocular findings progressed despite local therapy, and on September 2 the eye was proptosed and chemotic. A bruit was heard, maximal over the left eye, but radiating to all portions of the ipsilateral skull as well as to the contralateral frontal region, but not to the right eye. The bruit was diminished by ipsilateral carotid compression. Exophthalmometric readings at this time were 18 in the right eye and 23 in the left. There was no pulsation of either eye. Diagnosis of arteriovenous carotid cavernous fistula was made. On September 4, a left percutaneous angiogram was unsuccessfully attempted.

On September 8, 1952, a left open angiogram was performed under Pentothal anesthesia and 15 cc. of 35 per cent Diodrast was introduced into the left common carotid artery as rapidly as possible. Three lateral exposures were obtained; the first when 10 cc. of contrast medium had been introduced and the others at approximately two second intervals. The first exposure (figure 1) revealed filling of the internal carotid artery up to the level of the sella turcica. At this point an irregular collection of the contrast medium apparently represented the cavernous sinus. A large tortuous venous channel emerged from this region to divide into the superior and inferor ophthalmic veins in its course toward the orbit. Another large venous channel, the facial vein, was noted in its course

toward the angle of the mouth. In the temporal region, the vein of Labbé was filled with the contrast medium. None of the cerebral arterial circulation was demonstrated. On the second film of this series the internal carotid artery and the venous channels previously described were again noted, but the amount of contrast medium had diminished perceptibly as indicated by the decreased density of these vessels. On the third film, phlebography of the second phase, no evidence of contrast medium within the cerebral circulation remained. Within two hours after the procedure the patient became stuporous, developed a rectal temperature of 105°, and the blood pressure dropped to 70/33. There were no focal neurologic findings. Prompt therapy was instituted for shock, including caffeine, Coramine, nasal oxygen, and intravenous infusions. Three hours later the patient regained consciousness, blood pressure was 90/60, and rectal temperature dropped to 102°.

The bruit diminished and by the next day had entirely disappeared. Swelling and chemosis subsided within the succeeding four days, and the exophthalmometric reading of the left eye was 21. Ocular evaluation on October 12 showed further reduction to 20, and no other local abnormalities were present. Of interest was the observation that, with the subsidence of physical findings, a worsening of the mental state occurred and has persisted.

Re-examination on January 15, 1953 of the left cerebral arterial circulation (figure 2) demonstrated, on lateral view, the internal carotid artery and its division into the anterior cerebral artery and the middle cerebral artery. The branches of these two vessels were well demonstrated without evidence of pathologic change. The previously described arteriovenous aneurysm was no longer apparent, and there was no evidence of contrast medium within the venous circulation on the first arterial phase film. The second and third films revealed the normal second arterial phase and the first venous phase. An anteroposterior view revealed the left cerebral circulation adequately and without pathologic changes. The opinion was that the left cerebral angiogram was normal.

DISCUSSION

Wolff and Schmidt[5] indicated the six likely avenues of venous drainage from the cavernous sinus. They include the course: 1) through the superior and 2) inferior ophthalmic veins; 3) and 4) through the petrosal sinuses; 5) through the basal vein of Rosenthal, and via an anomalous vessel to the straight sinus and internal jugular system; and 6) up the sylvian vein or sphenoparietal sinus to ascend in the vein of Trolard.

In this patient angiography demonstrated the main venous drainage to be through the superior and inferior ophthalmic veins, and thence via the facial veins into the general circulation. The failure to delineate the cerebral arterial channels with alternative visualization of the cavernous sinus, ophthalmic, and facial veins during the usual "arterial phase," with the complete disappearance of the contrast medium from the cerebral circulation within approximately four seconds, could best be explained on the basis of a caroticocavernous communication. In addition, the Diodrast may have served as an irritant and vascular constrictor,[6] thus contributing to the spontaneous thrombosis of the communication[7–10] as is evidenced by the normal vascular pattern demonstrated in the second angiogram.

CONCLUSION

A case of carotid-cavernous fistula is presented in which spontaneous occlusion followed angiography. Angiograms before and after closure of the

communication are shown. It is inferred that the locally irritating and vasoconstrictor effect of the radiopaque medium utilized in the performance of angiography contributed toward thrombosis of the fistula.

REFERENCES

1. Lima, P. A.: A textbook of Cerebral Angiography, London, Oxford University Press, pp. 20-55, 1950.
2. Mense, J. S.: Carotid cavernous communication: A study of its causative mechanism and resultant angiographic patterns in the light of three personally observed cases, Bull. Los Angeles Neurol. Soc. 16:88, 1951.
3. Lock, E. E.: Intracranial arteriovenous aneurysm or pulsating exophthalmos, Ann. Surg. 80:1, 1924.
4. Rawling, L. B.: A Textbook of Head Injuries, London, Oxford University Press, pp. 15-32, 1934.
5. Wolff, H., and Schmidt, B.: Das arteriogram des pulsierender exophthalmus, Zentralbl. Neurochir. 4:241 and 310, 1939.
6. Foltz, E. L., Thomas, L. B., and Ward, A. A., Jr.: Effects of intracarotid Diodrast, J. Neurosurg. 9:68, 1952.
7. Abbott, K. H., Gay, J. R., and Goodall, R.: Clinical complications of cerebral and angiography, J. Neurosurg. 9:258, 1952.
8. Chusid, J. G., Robinson, F., Margules, G., and Lavergne, M. P.: Transient hemiplegia associated with cerebral angiography (Diodrast), J. Neurosurg. 6:466, 1949.
9. Dunsmore, R. H., Scoville, W. B., and Whitcomb, B. B.: Complications of angiography, J. Neurosurg. 8:110, 1951.
10. Raaf, J., and Swan, K.: Traumatic carotid cavernous sinus aneurysm, Am. J. Surg. 80: 816, 1950.
11. Harper, R. A. K., and Brit, J.: Radiologic changes in carotid-cavernous aneurysm, Radiology 12:150, 1943.
12. Himwich, H. E.: A Textbook of Brain Metabolism and Cerebral Disorders, Baltimore, Williams & Wilkins Co., pp. 91-124, 1951.

It only remains to point out what is the probable seat of the morbid action in the case of Megrim. Referring to his own attacks of transient half-vision, and to the fact on which we have so much insisted, that the visual field is similarly affected in both eyes, Dr. Wollaston justly observes that this must be owing to some source of disorder posterior to the decussation of the optic nerves, and probably in the Optic Thalamus: "Since the corresponding points of the two eyes sympathise from mere habit of feeling together, as might be inferred if reference were had to the reception of ordinary impressions alone. Any two corresponding points must be supplied with a pair of filaments from the same nerve, and the seat of a disease in which similar parts of both eyes are affected, must be considered as situated at a distance from the eyes at some place in the course of the nerves where these filaments are still united, and probably in one or the other Thalamus Nervorum Opticorum."

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

CLINICO-THERAPEUTIC DISCUSSION

An informal exercise, arranged by mail, to stimulate interest in treatment of neurologic disorders, and designed to be of practical value to physicians and students in all branches of medicine.

AUGUSTUS S. ROSE, M.D., *Section Editor*

Acute Generalized Muscular Weakness in an Eleven Year Old Girl

Case presented by
J. Sloan Berryman, M.D.

Discussion by
Douglas N. Buchanan, M.D.
Robert S. Schwab, M.D.
Lee M. Eaton, M.D.

CASE HISTORY

DR. J. SLOAN BERRYMAN
(Beverly Hills, California)

An 11 year old girl was seen in March 1953 as an emergency because of rapid development of profound muscular weakness, including difficulty in breathing. The mother stated that the child had been well until three weeks before. At that time she had a febrile illness termed the "flu," which lasted for several days. Recovery seemed complete. No special medication had been given. For the past three days she had complained of excessive fatigue in the afternoon and evening.

On the day of examination weakness had come on rapidly. Within a few hours she had had marked disturbance in breathing, spells of choking, and difficulty in swallowing and in speaking.

Examination showed a well developed, somewhat obese child, who was lying in bed with shallow, gasping respiratory movements. She was apprehensive, but alert and well oriented. There was bilateral ptosis, drooping of the jaw, and a blank, expressionless appearance to her face (figure 1). The voice was nasal in quality and barely audible. The facial muscles were weak, especially on the right. Saliva drooled from the mouth and there was difficulty in swallowing. She could wrinkle the forehead muscles weakly on the left; the palate lifted in midline and the tongue was protruded with almost normal strength. Extraocular movements were full and normal. Pupils, optic fundi, and sensation of face and pharynx were normal.

Grips were weak. Extremities and head could be lifted from the bed only with difficulty, and dropped back rapidly even though muscular contraction continued. Respiratory movements were labored but chest expansion was adequate. She was unable to sit up or turn over in bed without assistance. Muscular development was equal and normal. There was no fasciculation. The left triceps reflex and both ankle jerks were not obtained. Otherwise the tendon reflexes were present but sluggish. The abdominal reflexes were present; no response was obtained on plantar stimulation. Touch, pinprick, and movement of the extremities were properly appreciated.

The body temperature was normal and there were no significant findings on general physical examination.

Well documented case summaries presenting common treatment problems in neurology may be submitted to the editor of this section. Cases selected for publication will be sent to two or more neurologists for treatment recommendations and discussion.

FIG. 1. Patient showing the typical blank look and partly open mouth characteristic of myasthenia gravis. The ptosis formerly present has responded to medication.

A clinical diagnosis of acute myasthenia gravis was made, and she was given one ampule of neostigmine (1:2000) with atropine, gr. 1/150, intramuscularly. Because there was slight improvement after 15 minutes, two ampules of neostigmine were given intravenously. Strength improved but not dramatically. She was given several injections of neostigmine during the night. On the following day she was placed on oral medication.

Routine urine test was normal. Blood studies showed a red cell count of 4,810,000; hemoglobin 92 per cent; white cell count 8,800; smear normal. A roentgenogram of the chest was normal and showed no evidence of a thymus shadow.

The dosage of 30 mg. of oral neostigmine bromide and 0.6 mg. of atropine four times daily was gradually increased to 60 mg. of neostigmine every three hours while awake. After a short time muscular cramps became so severe and involuntary muscular contractions so violent that it was necessary to reduce the dose even though strength had not returned adequately. The addition of ephedrine sulfate, gr. ¾, four times per day caused increased nervousness and could not be continued at that time. A salt substitute containing potassium chloride was used liberally for her food. There was some gradual improvement. However, she was not able to be out of bed and short episodes of bulbar crises with dyspnea and choking developed which were relieved partly by oxygen administration. Difficulties in chewing and swallowing occurred from time to time.

About six weeks after beginning treatment, 500 mg. of guanidine hydrochloride in 4 tablets daily was added to neostigmine given in a dosage of 60 mg. every three hours. There then followed general improvement which seemed more like a clinical remission than response to medication. Although the patient continues to show flattened facies, ptosis, and drooping of the lower jaw, she is up and about most of the day, in a wheelchair at first, later on her knees, and recently walking with a cane. She has had no further difficulty in breathing and swallowing. She is being maintained on neostigmine bromide four tablets (60 mg.) four times daily, guanidine three tablets (375 mg.) four times daily, and sufficient atropine to control abdominal cramps. In addition, ephedrine gr. ¾ with phenobarbital gr. ¼ are occasionally added once or twice per day.

DISCUSSION

DR. DOUGLAS N. BUCHANAN
(Chicago, Illinois)

The clinical description would suggest acute infectious polyneuritis, as well as myasthenia gravis. Before therapy of any type should be discussed, every effort to establish the proper diagnosis is necessary. Until the cerebrospinal fluid is examined and its protein content and cellular reaction are known, the administration of large doses of neostigmine seems unwise.

If it is true that the child in question suffers from myasthenia gravis, her reaction to neostigmine is unusual. There are some children, as there are some adults, who respond to neostigmine by injection but later become resistant to this drug. It would be most unusual to find a child who did have myasthenia gravis and who was resistant to neostigmine the first time the medicine was used. Indeed, under these circumstances

it would be difficult to establish the diagnosis at all.

There is one way in which children with myasthenia react quite differently to appropriate drugs than adults. Many children in whom the diagnosis of myasthenia seems certain will, after a number of years, improve to such an extent that neostigmine is no longer needed. Some such children will improve to the extent that they become normal in all their physical activity and continue to be normal throughout the rest of their lives. Why this should happen is unknown. There is some evidence that it is correct at present to describe myasthenia as a symptom rather than a disease.

DR. ROBERT S. SCHWAB
(Boston, Massachusetts)

It seems unlikely from the history and from the response to neostigmine that any diagnosis other than myasthenia gravis can be entertained seriously. One must always keep in mind, however, that paralysis of the muscles of swallowing, weakness of breathing, and even weakness of the extremities may occur following acute nasopharyngeal diphtheria, which may go unrecognized when mild. But it is usual in that condition to have sensory symptoms or signs, cardiac involvement, and disturbance in papillary reactions. None of these abnormalities were recorded in this patient. In support of the diagnosis of myasthenia are the type of onset, improvement with rest, response to parenteral neostigmine, and maintenance of improvement when changed to oral administration.

The following comments may be made concerning medication:

1. The necessity in this case for giving atropine, which sometimes may be tolerated poorly, indicates that the dosage of neostigmine may be too large. It might be better to administer the neostigmine in smaller doses more frequently. For example, less atropine may be required and better therapeutic effect obtained if 30 mg. of neostigmine were given every one and a half hours in place of 60 mg. every three hours. Sometimes less atropine is needed if liquids are administered with each dose of oral neostigmine.

2. Improvement in myasthenic symptoms following the addition of guanidine is, in our experience, a relatively rare phenomenon, occurring no more frequently than about one in ten cases. Apparently, guanidine was distinctly beneficial in this case.

3. Because the myasthenic signs have persisted, it is probable that this child would benefit from a larger total daily dose of neostigmine.

Patients in this age group commonly go into remission upon the removal of the thymus, even though no thymic shadow is visible on x-ray examination. One can say statistically that about two-thirds of young females clearly benefit by thymectomy, as shown in several large series of such operations. This is not true in males or in older females. Should such a procedure be considered for this patient, it is mandatory that a better level of muscular strength be obtained by regulation of medication.

DR. LEE M. EATON
(Rochester, Minnesota)

First of all, it is unusual for a patient who has myasthenia gravis to become weakened to the extent described within a period of three days. However, the response to administration of neostigmine as reported is sufficiently characteristic to be diagnostic of myasthenia gravis. Had the patient been ill with poliomyelitis, polymyositis, neuronitis, or a condition producing hypopotassemia, the administration of neostigmine would not have resulted in unequivocal improvement in muscular strength and function.

In my opinion, the problem has been handled well, and the attending physi-

cian is to be congratulated on his recognition of the true nature of the illness.

Particularly in patients as severely ill as this one, we have found nothing superior to neostigmine in treatment. The administration of potassium, guanidine, and octamethyl pyrophosphoramide (OMPA), sometimes of value in the treatment of ambulatory patients, is likely to complicate treatment of the patient in crisis. The amount of neostigmine given orally or parenterally which produces the maximum of improvement in strength and the minimum of complications is arrived at by trial and error. The individual doses are administered as frequently as experience shows is necessary to maintain the maximal level of improvement. It is possible in this case that two or three tablets of neostigmine taken every one and a half to two hours might be better than four tablets of neostigmine every three hours. The administration of atropine to prevent undesirable gastrointestinal symptoms, and ephedrine in an attempt to enhance the effect of neostigmine, is approved.

In the present state of our knowledge, thymectomy is indicated in this case, provided the condition of the patient does not contraindicate it. Since the patient is improving steadily, it is possible and perhaps probable that satisfactory remission will occur. Consequently, if thymectomy is to be done, the problem posed by this case lies in selecting the time for surgical interference. As long as the patient continues to improve, I would be in no hurry to intervene surgically. When and if the patient reaches that stage of recovery in which, while taking the optimal amount of neostigmine, she can cough with vigor and has no significant difficulty in swallowing or expectorating secretions from the throat, surgical treatment can be undertaken without great risk. I should estimate the risk of surgical treatment in experienced hands under these conditions at $3\pm$ per cent mortality. Should the improvement fail to reach this level, the risk of surgical treatment would be considerably higher in spite of tracheotomy and meticulous postoperative care. It then becomes a question of weighing one risk against the other; the risk of operative death against the risk of death from myasthenia gravis.

Should complete remission follow thymectomy in this particular case, it will not be possible to attribute the good result to removal of the thymus gland, since the acute onset followed by gradual spontaneous improvement is indicative of a good prognosis.

Should spontaneous improvement cease leaving the patient seriously ill, it might be well to consider irradiation of the thymus gland.

The administration of ACTH has given disappointing results in our cases. Use of this agent should not be attempted during a stage in which the temporary aggravation of symptoms would be hazardous.

CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.
Section Editor

Presented by H. Houston Merritt, M.D. and Abner Wolf, M.D.

CASE PRESENTATION

A 43 year old automobile mechanic was transferred from another hospital with the chief complaint of "paralysis of both legs."

History: In November 1951, while lying on his side to repair a car, the patient was kicked in the low back area. There were no immediate symptoms except for slight soreness in the region. Several days later he had a sensation of coldness and numbness, spreading from the right hip to the lateral aspect of the right thigh, leg, and foot. Gradual weakness of that extremity began after this episode. A few weeks later a similar sensation of coldness and numbness was noticed spreading band-like from the right hip to the left hip and down the left leg. Two months after onset of the present illness he had difficulty in starting urination. This was followed in a short time by urinary incontinence and constipation. On July 1, 1952 he was admitted to another hospital with complaints of weakness, paresthesias, and involuntary movements in both legs. At that time he was still able to walk, though his legs occasionally buckled under him. The illness grew progressively worse, both legs became paralyzed, and he was anesthetic below the level of the lower sternum. Laboratory studies in the previous hospital were as follows: Five lumbar punctures showed total cerebrospinal fluid proteins ranging from 140 to 1800 mg. per cent; sugar from below 10 to 25 mg. per cent, and chlorides between 660 and 695 mg. per cent. Smears and cultures of the cerebrospinal fluid were negative for bacteria, fungi, and acid-fast bacilli. Colloidal gold curve was normal. Chest and skull roentgenograms were negative. The myelographic report from the other hospital stated, "In the upper dorsal regions the appearance in scattered segments suggests an arachnoiditis."

A few weeks before transfer the patient started feeling some occasional numbness and tingling in both hands. He also complained of frequent headaches, stiffness of the neck, and pain on moving his head from side to side. According to the patient, all of these symptoms appeared after the lumbar punctures and myelogram.

Past history and family history were not significant.

Physical examination: On admission he was a cooperative alert male who was emaciated, generally weak, and looked chronically ill. His complexion was quite pale. There was photophobia and nuchal rigidity. Examination of the thorax, abdomen, skin, and lymph nodes showed no abnormalities. Temperature was 98° F., pulse 120 and regular, respirations 28, and blood pressure 124/88.

Neurologic examination: There was complete paralysis of both legs. No voluntary movements of the legs were possible but there were occasional irregular contractions of various muscle groups. All muscles of the thighs, calves, and feet showed marked

From the department of neurology and the division of neuropathology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute, Presbyterian Hospital, New York City.

atrophy and muscle tone was diminished. Strength in the arms was normal. Reflexes were decreased in the arms and slightly hyperactive in the legs. Abdominal and cremasteric reflexes were absent. Babinski's, Chaddock's, and Oppenheim's signs were present bilaterally. Touch, vibration sense, position sense, and pain and temperature sensation were absent in the right leg and a portion of the right lower trunk and markedly diminished in the left leg and left lower trunk. The level of sensory impairment was as high as the xiphoid process. There was sparing of the left saddle area where sensation was only slightly decreased. Stereognosis and palm-writing were normal. Cranial nerves were apparently normal except the disk margins on the right were not as sharply outlined as on the left. Mental status was not unusual.

Laboratory examination: Blood: hemoglobin 14.7 gm.; white blood cells 12,000 (90 per cent polymorphonuclear cells, 10 per cent lymphocytes); Mazzini, negative. Urine: 1+ albuminuria, 10 to 15 red blood cells per high power field. Lumbar puncture: initial pressure 310 mm.; manometrics showed a complete block; fluid was xanthochromic and contained 3 white blood cells and 31 fresh red blood cells per cu. mm.; total protein was 3700 mg. per cent; sugar 37 mg. per cent; chlorides 641 mg. per cent; colloidal gold curve: 4432110000; cultures and smears were negative for bacteria, acid-fast bacilli, and fungi. Cisternal puncture, done one day after the lumbar puncture, showed a total protein of 576 mg. per cent; sugar 28 mg. per cent; chlorides 666 mg. per cent; 3 white blood cells and 10 fresh red blood cells per cu. mm.

Lumbar myelogram showed an obstructing lesion at the level of T8 to T9. The cisternal myelogram suggested an extramedullary tumor at T8 to T9, but there was an irregular spread of Pantopaque throughout the length of the canal which could have been caused by an inflammatory process or by multiple cyst formation.

Course in hospital: The patient's temperature stayed between 97.4° and 99.6° F. There were no marked fluctuations in other vital signs. On the seventh hospital day he seemed confused, had a visual hallucination (trees), and was disoriented. These aberrations in mental status persisted. Laminectomy and intradural exploration were done on the fifteenth hospital day. His condition remained unchanged until the third postoperative day when he suddenly became comatose, had gasping respirations, and expired.

CLINICAL DISCUSSION

DR. MERRITT: It is clear from the history and findings that a definite diagnosis cannot be made. However, the possibilities can be narrowed down to several distinct entities. In reviewing the history it is obvious that the patient had an intraspinal mass at about the level of the eighth thoracic segment and that, in addition, he had a diffuse involvement of the meninges. The mass in the thoracic region readily explains the patient's paralysis, sensory findings, and reflex disturbances. It does not, however, account for the mental symptoms and changes in the cerebrospinal fluid. In all probability these were related to a diffuse involvement of the leptomeninges. The significant cerebrospinal fluid findings are the high protein content and low sugar values. Elevated protein in the lumbar cerebrospinal fluid could be a result of the block, but the block would not explain the high protein content in the cisternal fluid. The low sugar content in the lumbar and cisternal fluids can only be accounted for on the basis of a meningitis or infiltration of the meninges with neoplastic cells.

With these considerations in mind, I would like to limit the discussion to three conditions: 1) tuberculoma of the spinal cord with tuberculous meningitis; 2) torula granuloma of the spinal cord with torula meningtis; and 3) neoplasm of the spinal cord with diffuse neoplastic involvement of the meninges.

Tuberculomas of the spinal cord are relatively rare in this country at the present time. The spinal fluid findings, however, were compatible with the diagnosis of tuberculous meningitis, but the duration of the active phase of the meningitis is against this diagnosis. It is noted that the spinal fluid was abnormal when the patient was studied at another hospital

as early as July 1, 1952 and the patient did not die until October 24, 1952. At no time did he receive any streptomycin or other antitubercular drugs. In addition, cultures of the spinal fluid for tubercular bacilli were negative on many occasions. There is no mention of guinea pig inoculation.

The second possibility, that of torula meningitis with localized granuloma formation in the spinal cord, seems more probable. The spinal fluid findings are compatible with this diagnosis and the duration of the disease is not unusual. We have no confirmation of this diagnosis because all cultures of the spinal fluid on Sabouraud's medium were negative. This does not, however, exclude the diagnosis.

The third possibility is diffuse neoplastic invasion of the meninges with local tumor formation in the lower thoracic region. It is now well-known that diffuse involvement of the meninges with carcinomatous, sarcomatous, or gliomatous cells may be accompanied by a reduction in the sugar content of the cerebrospinal fluid.[1,2] In the majority of these cases, however, there is a primary focus in the central nervous system or elsewhere in the body and only rarely is the involvement limited to the meninges. There was no evidence in this patient of a carcinoma in the lung or elsewhere in the body, nor was there any indication that the patient harbored a glioblastoma or medulloblastoma in the brain.

We can only repeat the statement made at the introduction to the effect that no clinical diagnosis can be established with certainty in this case. I would list the most probable diagnoses in the following order: 1) diffuse infiltration of the meninges with neoplastic cells, with a nodule compressing the thoracic cord; 2) torula meningitis with granuloma formation in the spinal cord.

Anatomic Diagnoses: Glioblastomatosis of cerebrospinal leptomeninges with extension to spinal cord, brain stem, cerebellum, and cerebrum.

Pneumonia, lobular, left lower lobe.
Bronchitis, acute.
Fibrosis, pulmonary, moderate.
Emphysema, pulmonary, slight.
Arteriosclerosis, aorta, moderate.
Hypertrophy, myocardium of left ventricle.
Congestion, passive, lungs, liver, spleen, adrenals and kidneys.
Calculi, urinary bladder.
Cystitis, urinary bladder, chronic.

PATHOLOGIC DISCUSSION

DR. WOLF: This was a remarkable instance of diffuse glioblastomatosis of the cerebrospinal leptomeninges. The most striking findings were those in the meninges about the spinal cord. From the level of the cervical enlargement down to the sacral segments, there was a series of irregular white opacities in the leptomeninges partially obscuring the underlying spinal cord. These were more numerous and prominent upon its dorsal aspect where they were also protuberant, nodular, and firm and coalesced into larger masses. The greatest of these measured 2¼ x 2 x 0.4 cm. and lay upon the surface of the ninth thoracic segment. Other smaller masses were present on the surfaces of the lower thoracic and upper lumbar segments. Tiny nodules of tumor studded the leptomeningeal surfaces of the conus medullaris. Elsewhere a more diffuse sheet of milky opacity resembling a meningitis marked the spread of the neoplasm in the spinal leptomeninges. A firm, slightly protuberant, whitish opacity measuring 0.6 cm. in diameter was seen in the leptomeninges over the anterior hypothalamus. Another smaller nodule was present in the leptomeninges over the right inferior semilunar lobule.

On section of the spinal cord, superficial invasion of the white matter was noted, deep to some of the larger leptomeningeal masses. In some instances the invasion penetrated more deeply. This

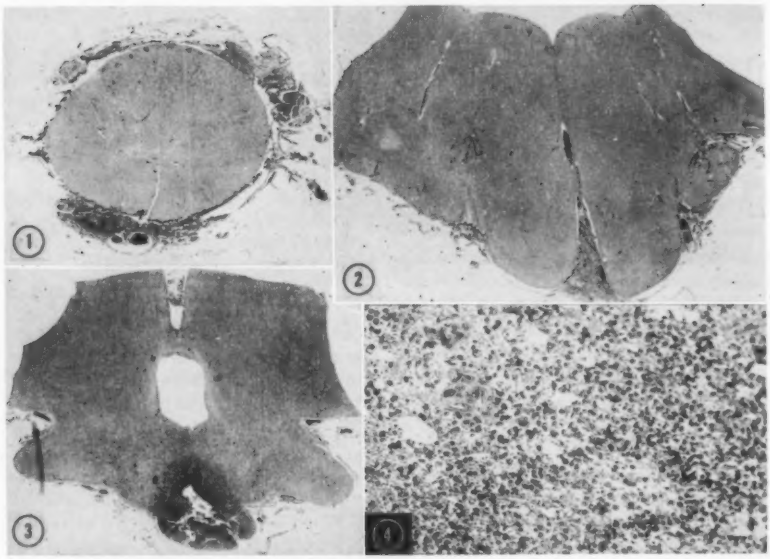


FIG. 1. Glioblastoma in leptomeninges about spinal cord with slight superficial invasion of posterior columns.
FIG. 2. Glioblastoma in leptomeninges at junction of pons and medulla.
FIG. 3. Glioblastoma in basilar leptomeninges and hypothalamus.
FIG. 4. Glioblastoma in leptomeninges showing high cellularity, cell variety, focal necrosis, and pseudo-palisade formation. All specimens stained with hematoxylin and eosin.

was true of the hypothalamic nodule, as well. Histologically, this neoplasm was highly cellular and of similar morphology wherever it was encountered. Microscopically it was seen in the leptomeninges at every level of the neuraxis examined. The neoplastic elements were variable in their morphology. They included small cells with scanty cytoplasm and oval, deeply staining nuclei, elongated bipolar cells, larger irregular or polygonal cells with more abundant cytoplasm and eccentric oval nuclei, and some multinucleated cells. Special stains revealed glial fibers emanating from and lying between tumor cells. Mitoses were frequent and focal necroses occasional. Many of the small tumor vessels showed mural cell hyperplasia. In places the invaded leptomeninges exhibited a reactive fibrosis. Secondary degeneration in the gray and white matter of the spinal cord was chiefly consequent to invasion of nerve roots by tumor and to compromising of leptomeningeal vessels.

As in previous instances of such diffuse gliomas in the leptomeninges, the problem is presented whether the tumor arose within those membranes or from foci in the parenchyma from which it spread widely. This question is difficult to resolve. Some large foci of tumor growth within the parenchyma are found in the thoracic cord which might conceivably be the point of inception of the neoplasm. The clinical history, however, would not support this view. If this is not the site of the first growth of the tumor, then one might seek in many of the small superficial nodules of tumor tis-

sue seen elsewhere as the areas in which the tumor began. However, this seems highly unlikely since the histologic appearances suggest very strongly that the tumor invaded these zones from the leptomeninges. The other possibilities are that it arose from such a structure as the filum terminale as do ependymomas in the lumbar sac, but direct evidence of this is not available. This tumor may have arisen from intraleptomeningeal glial nests or glial heterotopias such as are sometimes encountered in cases of multiple malformations of the central nervous system and its envelopes. That this was essentially a leptomeningeal neoplasm in its final phases is beyond question. There was widespread involvement of nerve roots and of cranial nerves. One secondary effect on the parenchyma from the radicular involvement was a central chromatolysis of anterior horn ganglion cells. There was considerable myelomalacia in the areas heavily invaded by tumor in the thoracic region. The invasion of the hypothalamic region may have led to some of the patient's terminal symptoms, while the widespread secondary involvement of the cerebral cortex from the leptomeninges probably produced the terminal mental difficulties.

REFERENCES

1. Strange, L. F.: Metastatic carcinoma to the leptomeninges, Tr. Am. Neurol. A. 79:181, 1952.

2. Berg, L.: Hypoglycorrhachia of noninfectious origin: Diffuse meningeal neoplasia, Neurology 3:811, 1953.

Convulsions often attend the onset of an acute cerebral lesion, or occur during the early stages of the lesion. They may occur, for instance, at the onset of cerebral hemorrhage, or cerebral softening from vascular occlusion, but the lesion which causes the convulsions causes also other obtrusive symptoms, usually hemiplegia, which declare its existence. A convulsion beginning unilaterally may cause transient hemiplegia; and if the convulsion is the first from which the patient has suffered, a doubt may exist as to whether both convulsion and paralysis are not the result of an acute cerebral lesion. The weakness succeeding the hemiplegia very rarely amounts to complete paralysis; it is most marked in the limb (arm or leg) in which the fit commenced; and it passes away in the course of a few hours. When, on the other hand, the convulsion and paralysis are the result of an acute lesion, the paralysis is usually at first complete; it affects both arm and leg, and it scarcely ever passes away in the course of a few hours, usually lasting for days or weeks. In most cases, however, the patient has had other fits beginning unilaterally, and then, especially if the paralysis is incomplete, the diagnosis of post-epileptic hemiplegia may be made with confidence. In cases of softening from vascular obstruction, convulsions may occur a few days or a week after the onset, apparently from the adjacent irritation consequent on the strain upon the collateral vessels. In these cases, the convulsions succeed paralysis, and the diagnosis of their cause presents no difficulty.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

CASE REPORT

Traumatic Pneumocrania and Subdural Spinal Fluid

Ardis Storm-Mathisen, M.D.

THE following case appears to be of sufficient rarity and clinicopathologic interest to warrant publication.

CASE REPORT

A dock worker, born September 20, 1897, was the victim of a severe head trauma on October 28, 1952. During work he fell headlong off the wharf, his head being compressed between the wharf and the side of a freighter. There was loss of consciousness for about two hours, with anterograde and retrograde amnesia. On admission to the hospital about one hour after the accident, the patient suffered from shock. He was bleeding from the right ear and from both nostrils.

X-ray examination of the skull two hours after the accident disclosed several fractures. On the right side one fracture was seen in the middle cranial fossa and one in the temporal bone. Further, a fracture was seen at the base of the dorsum sellae, particularly distinct on the left side (figure 1). However, the most striking finding on routine x-ray examination was air in the ventricles of the brain, together with subarachnoid and subdural air (figure 2). The subdural air was distinctly present three days after the accident. On control examination ten days after the trauma the subdural air had disappeared; the intraventricular air, however, was present, though substantially reduced in quantity. Nineteen days after the accident the intraventricular air had also disappeared.

Neurologic examination demonstrated bilateral abducens and facial paralysis and neurogenic reduction of hearing on both ears. These findings still persist nine months after the trauma. Bilateral peripheral facial paralysis was accompanied by pronounced atony of the mimic muscles of the face. The eyelids and the region of the mouth sagged flaccidly, the lower lip being everted (figures 3 and 4). The latter figure also demonstrates bilateral impairment of the sixth cranial nerve. Tarsorrhaphia was performed bilaterally.

Due to facial paralysis the patient had difficulties in eating, and liquid food ran out of the mouth. This case illustrates distinctly a dysarthria which is exclusively a result of bilateral facial paralysis. It particularly involves the consonants: *b*, *m*, *p*, *v*, and *w*, but the pronunciation of *f* and of vowels is also difficult. The patient has gradually taught himself certain tricks of speech. Thus he pushes the lower jaw forward and supports the lower lips with the hand, at the same time inclining the head backward. Nevertheless, the dysarthria is evident.

The case is striking for the reason that the bilateral lesion of the sixth, seventh, and eighth cranial nerves not only makes him unfit for work, but also isolates him

From the department of neurology, Oslo City Hospital (Ullevål Hospital), Oslo, Norway.

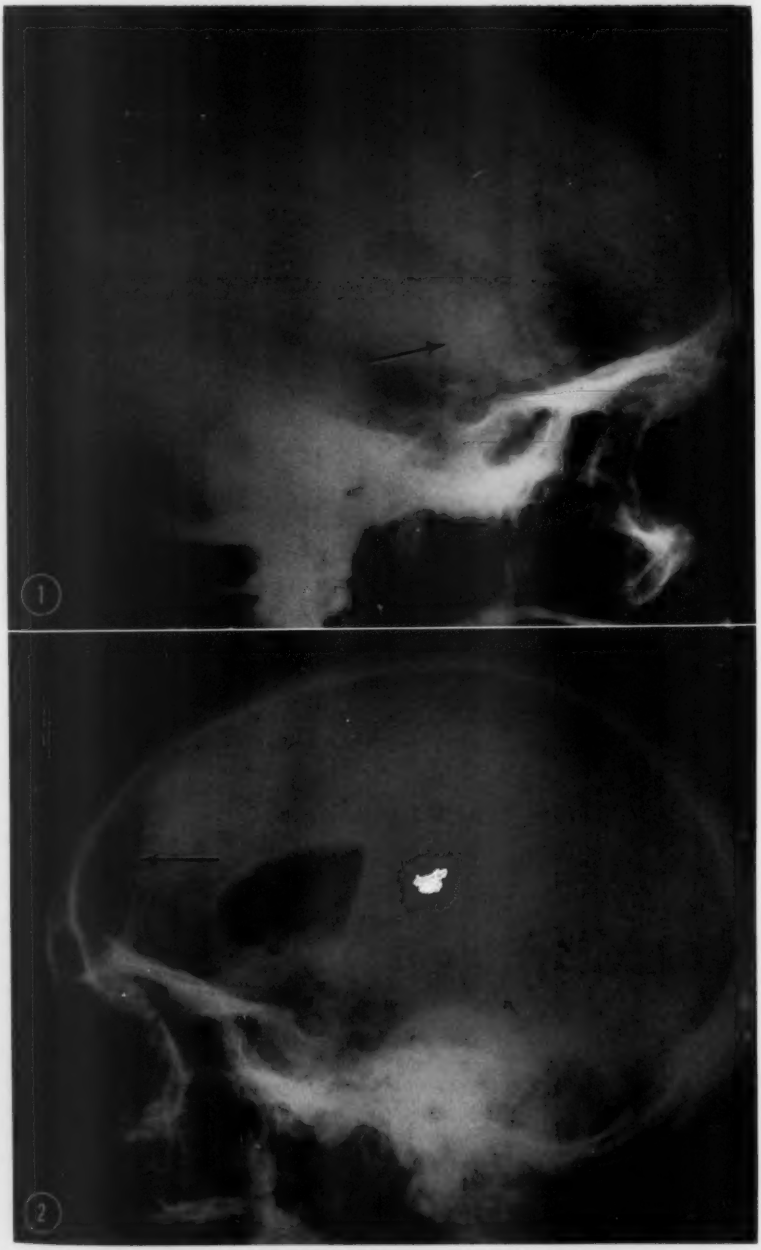


FIG. 1. Roentgenogram of the skull showing fracture at the base of the dorsum sellae.
FIG. 2. Routine roentgenographic examination reveals pneumocrania with intraventricular and subdural air, from which the brain rises calotte-shaped through a horizontal level of spinal fluid. A horizontal intraventricular fluid level is also demonstrated.

FIG. 3. Peripheral facial paralysis accompanied by pronounced atony of the mimic muscles. The eyelid and the region of the mouth sag flaccidly and the lower lip is everted.
FIG. 4. Peripheral facial paralysis with marked atony of the mimic muscles. Bilateral impairment of the sixth cranial nerve is also demonstrated. Tarsorraphia is performed bilaterally.

from the environment, making him a lonely man. The patient has not complained of the common late sequelae following considerable concussion of the brain, such as headache and dizziness.

COMMENT

The x-ray findings are of particular interest. Routine x-ray examination two hours after the accident revealed subarachnoid and subdural air, as well as symmetrical air-filling of the ventricles of the brain.

Pneumocrania is rare in the presence of fracture of the skull. This condition was reported first in 1913 by Luckett,[1,2] later by Holmes[3] in 1918, and by May,[4] Potter[5] and Glenard and Aimard[6] in 1919. The condition was also described by Ingebrigtsen in 1942.

The criteria for occurrence of pneumocrania in fracture of the skull are 1) that the fracture passes through pneumatized bones and 2) that the dura, or the dura and the arachnoid, are ruptured simultaneously. It is possible also that increased pressure is necessary to press the air through the fracture slits (for example, when the patient is coughing or sneezing).

There are two forms of pneumocrania depending on whether the dura only, or the dura and the arachnoid, are severed. In the first instance, air may pass into the potential subdural space between the dura and the arachnoid. Radiographically, a continuous air-mantle is seen at the highest level of the cranial cavity. The brain and arachnoid drop away from the dura, and the contour of the brain may be observed in the lower part of the air-mantle, as shown in figure 5. This finding demonstrates direct subdural air-filling such as might be brought about by allowing a needle to

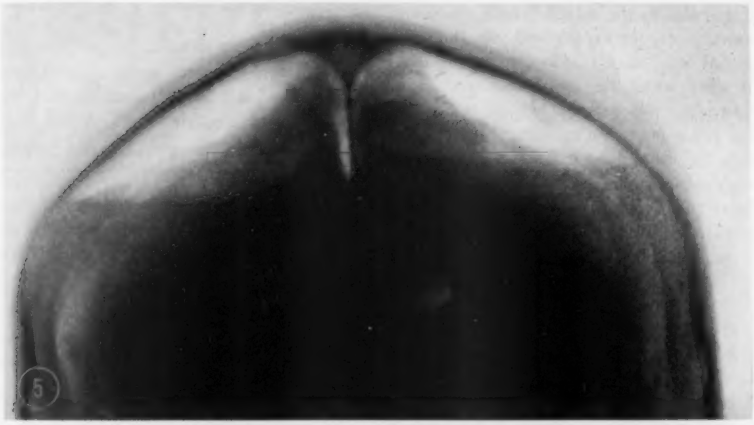


FIG. 5. Direct subdural air-filling brought about by allowing the needle to pierce the dura only, not the dura and arachnoid as in ordinary pneumencephalography. A continuous air mantle is seen at the highest level of the cranial cavity. The contour of the brain is observed in the lower part of the air mantle. Air seen in the ventricles is residual air after an ordinary pneumencephalography performed eight days before the direct subdural air-filling. The ordinary pneumencephalogram did not show subdural air.

pierce the dura only and not the dura and the arachnoid as in ordinary pneumoencephalography. In the latter instance, when both the dura and arachnoid are ruptured, it is possible for air to enter the subarachnoid space, the subdural space, and the ventricles of the brain. Spinal fluid may penetrate the arachnoid and fill part of the subdural space. The present case of pneumocrania demonstrates this second form, with intraventricular and subarachnoid air and a distinct mantle of subdural air from which the brain rises calotte-shaped through a horizontal level of spinal fluid (figure 2).

Occasionally subdural intracranial air is seen by routine endolumbar air encephalography,[8,9] particularly in patients who had a previous head trauma. In some cases only subdural air-filling occurs; in others air may be observed in the subarachnoid space and in the ventricles of the brain in addition to subdural air.[10]

Such subdural air may be due either to direct introduction of air into the subdural space, or to the fact that the air, after having been injected into the subarachnoid space in the routine manner, may pass further subdurally through rents in the arachnoid, which normally is impermeable to air, even under considerable pressure. Several authors, therefore, have ascribed the occurrence of subdural air after an endolumbar pneumoencephalography to injuries of the arachnoid.[11] At the Oslo City Hospital, pneumoencephalography has been carried out in a few cases a couple of days after concussion of the brain (without fracture), and subdural air has been demonstrated.[7]

These experiences may assist in finding an explanation of part of the mechanism of concussion of the brain and its sequelae. When the skull is subjected to more severe blows, movements occur between the skull and the cerebral surface, resulting in severance of the fine

trabeculae in the subarachnoid space and tearing of the arachnoid so that the spinal fluid may trickle out subdurally.[7] In this way, the arachnoid may drop down on the surface of the brain and the brain may lose its natural fixation inside the cranial cavity. Thus the normal cerebral mechanism of stabilization will be out of function and the conditions of circulation in the cranial cavity will be disturbed. It is possible that some of the complaints of vertigo and nausea that often accompany movements of the head immediately after concussion of the brain may be attributed to this pathologic mechanism. During such conditions damage to the arachnoid air will penetrate tears in the arachnoid and pass into the subdural space. After some time the arachnoid tears will heal, and if air is then inflated in the ordinary manner subdural air will not be observed.

SUMMARY

Routine x-ray examination of the skull immediately following a major head trauma showed air in the ventricles of the brain, together with subdural and subarachnoid air. The mechanism of pneumocrania is discussed.

An attempt has been made to explain the mechanism of concussion of the brain as arachnoid rupture with secondary outflow of spinal fluid into the subdural space.

The neurologic findings after a severe head trauma were bilateral lesions of the sixth, seventh, and eighth cranial nerves, resulting in difficulties in eating and speaking, and making the patient unfit for work. The usual posttraumatic complaints such as headache and dizziness were not present.

REFERENCES

1. Luckett, W. H.: Air in the ventricles of the brain following a fracture of the skull, J. Nerv. & Ment. Dis. 11:326, 1913.
2. Luckett, W. H.: Air in the ventricles of the brain following fracture of the skull, Surg., Gynec. & Obst. 24:362, 1917.
3. Holmes, G. W.: Intracranial aerocele following fracture of the frontal bone, Am. J. Roentgenol. 5:384, 1918.
4. May, R. J.: Report of a case showing air within the cranial cavity, Am. J. Roentgenol. 6:190, 1919.
5. Potter, H. E.: A case of hydro-pneumocranium with air in the ventricles, Am. J. Roentgenol. 6:12, 1919.
6. Glenard, R., and Aimard, J.: Aérocèle traumatique, du cerveau, Presse méd. 27:123, 1919.
7. Ingebrigtsen, B.: Personal communication.
8. Lemere, F., and Barnacle, C. H.: Encephalography: A review of eight hundred encephalograms with special reference to subdural air, Arch. Neurol. & Psychiat. 35:990, 1936.
9. Kristiansen, K.: Neurological Investigations of Patients with Acute Injuries of the Head, Oslo, Jacob Dybwad, 1949, pp. 46-50.
10. Cramer, F.: A note on the occurrence and significance of air in the subdural space after encephalography, Bull. Neurol. Inst., New York 3:506, 1934.
11. von Storch, T. J. C., and Buermann, A.: Subdural shadows in pneumoencephalograms: Their diagnosis, origin and significance, Arch. Neurol. & Psychiat. 42:810, 1939.

NEWSLETTER

JANUARY, 1954

Howard D. Fabing, President
Walter O. Klingman, President-Elect
Francis M. Forster, Vice-President
Alexander T. Ross, Secretary
Dave B. Ruskin, Treasurer

AMERICAN ACADEMY OF NEUROLOGY

New Review Courses Planned for AAN Meeting in Washington The popularity of review courses in special neurologic fields at AAN annual meetings has led the special courses committee to organize an entirely new group of courses to be given April 26 to 28, immediately preceding this year's annual meeting of the Academy at the Shoreham Hotel, Washington, D. C. Among them are special courses on coma, diseases of the spinal cord, and disorders of the hypothalamus. A new course in neurophysiology, which has been in careful preparation for the past two years, is also offered and will cover a two day period. ... In addition, the short course on headache, given last year by Dr. Arnold Friedman, will be repeated. A one day review course in neuropathology will again make available to members and others the AAN loan collection of neuropathologic slides.... An outline of the content of each course, application forms, and fee schedules may be obtained from Dr. A. B. Baker, Chairman, Committee on Special Courses, American Academy of Neurology, 19 Millard Hall, University of Minnesota, Minneapolis 14.

Scientific Exhibits Benjamin Boshes announces a promising array of scientific exhibits and demonstrations for the annual AAN meeting in Washington. The program is being planned carefully to place the exhibits in strategic points exposed to the greatest flow of membership traffic.... Applications for the presentation of scientific exhibits should be accompanied by a title and descriptive abstract of 100 to 150 words. The deadline for titles and abstracts is January 15, 1954. All communications should be forwarded to Benjamin Boshes, Chairman, Committee on Exhibits, Department of Nervous and Mental Disease, Northwestern University Medical School, 303 East Chicago Avenue, Chicago 11.

Panel of Science Writers Invited to Participate in AAN Meeting Through the AAN public relations committee, a letter has been written to a panel of distinguished science writers inviting them to make recommendations on a proposed special conference of neurologists and science writers to be

held at the 1954 annual meeting. Such a conference would give science writers an opportunity to submit questions of interest in the neurologic field in advance to appropriate specialists for reply and discussion. Because of the already tight schedule of scientific sessions, such a meeting, if agreeable to the Academy and the press, would be held in the evening, possibly Thursday, April 29.

The Shoreham Is World Famous Hostelry The Shoreham Hotel, headquarters for the 1954 annual AAN meeting, has world renown as a focal point for important gatherings and distinguished personalities. While primarily a transient hotel, it is the permanent residence of many congressmen and U. S. senators and of many foreign representatives to this country. It is rare not to see one of the country's legislators walking along the corridors or sitting in one of the lounges on almost any day of the week.... All rooms are large, well-decorated, and look out on one of the pleasant residential sections of Washington. Yet the hotel is within ten minutes reach of the shopping centers and historic landmarks of the nation's capital. The Shoreham has many dining rooms and a cuisine whose reputation is esteemed. There is dancing at both the Palladian and Blue Rooms, and, if weather permits, the outdoor terrace affords a gracious chance for both dining and dancing.

* * * * * *

Conference on Cerebral Vascular Disease to be Held in Princeton To bring into sharper focus the medical and socio-economic significance of cerebral vascular disease, thirty outstanding investigators and clinicians from several disciplines will convene at the Nassau Tavern in Princeton, N. J., January 24 to 26. The conference is sponsored by the American Heart Association under the chairmanship of Dr. Irving S. Wright, professor of clinical medicine, Cornell University. The conference will take the form of round table discussions, following brief introductory statements of the fundamental problems of cerebral vascular disease from the standpoint of neurology, neurosurgery, psychiatry, internal medicine, rehabilitation, and the basic sciences. All material emanating from this conference will be transcribed, edited, and prepared for publication in book form. It is hoped that the conference will present the problem as it now exists and the questions which need to be answered in the future in this relatively neglected field of medicine.... Among the participants will be Raymond D. Adams, Paul C. Bucy, H. H. Jasper, S. S. Kety, H. W. Magoun, H. Houston Merritt, C. H. Millikan, Howard Rusk, R. S. Schwab, G. von Bonin, H. G. Wolff, Irving S. Wright, and H. M. Zimmerman.

ARNMD Meets in New York The Association for Research in Nervous and Mental Disease held its thirty-third annual meeting at the Hotel Roosevelt, New York City (December 11-12, 1953). The subject under consideration was "Genetics and the Inheritance of Integrated Neurological and Psychiatric Patterns." The field covered was large, ranging from general principles of human genetics to particularized studies in heredity and embryology.... President of the 1953 commission was Davenport Hooker of Pittsburgh.

A.M.A. Clinical Meeting Held in St. Louis The annual clinical sessions of the A.M.A. were held in St. Louis, December 1 to 4; Henry R. Viets presided over the general sessions. As customary, the tenor of the program was clinical and practical, and neurology was well represented. Such subjects as the "Differential Diagnosis of Strokes" (Sahs), "Clinical Significance of the Electroencephalogram" (O'Leary), "Thyroid Disease and the Nervous System" (Levy), and the "Symptoms and Signs of Brain Tumor" (Schwartz) were included among the neurologic papers. These were supplemented by several interesting exhibits such as "Uses of EEG in General Practice" (O'Leary), "Management and Diagnosis of Myasthenia Gravis" (Osserman and Kaplan), "Neurogenic Arthropathy" (Mead), and "Control of Side-Effects of Anticonvulsant Drugs" (Schwab).

* * * * * *

Neurologic Training Grants Awarded to Medical Schools The Advisory Council to the National Institute of Neurological Diseases and Blindness and the Surgeon General of the Public Health Service have approved the institute's first grant awards to medical schools and teaching hospitals for graduate training in neurology and ophthalmology in the amount of $400,000. The purpose of this program is to provide increased graduate training facilities in non-federal institutions for physicians who wish to teach and pursue academic careers in these fields. The institutions which were awarded such grants were: Georgetown University (neurology), State University of Iowa (neurology), University of North Carolina (neurology), University of Vermont (neurology), Albany Medical College (neurology), University of Utah (neurology), Harvard Medical School (ophthalmology), Ohio State University (ophthalmology), University of Chicago (neurology), University of Oregon (ophthalmology), Western Reserve University (ophthalmology), Johns Hopkins University (ophthalmology), Columbia University (neurology), University of Kansas (neurology), Washington University (neurology and ophthalmology), and Northwestern University (neurology). Applications for such grants were far in excess of the Institute's appropriation for this purpose.

Briefs The Muscular Dystrophy Clinic at the Georgetown University Hospital was formally opened by Mr. Richard Woods, president, Washington Chapter of the Muscular Dystrophy Association. This clinic is under the immediate supervision of Tiffany Lawyer, Jr., assistant professor of neurology at Georgetown.... Joseph Wilder announces the availability of approved residencies in neurology at Goldwater Memorial Hospital, New York City. His associate in this program is Dr. Milton Tarlau. ... The first annual meeting of the Myasthenia Gravis Foundation was held at the Hotel Roosevelt, New York City on December 11.... Dr. Leonard Bell Cox of Melbourne, Australia, an authority on torulosis and classification of brain tumors, is making a study of the organization of various neurologic institutes in the U. S. preparatory to setting up an institute in Melbourne.... Dr. Louis Casamajor, professor emeritus of clinical neurology at Columbia University and consultant to the Presbyterian Hospital, was one of 25 individuals who received distinguished service awards in connection with the twenty-fifth anniversary of the Columbia-Presbyterian Medical Center, October 12-13, 1953.... A one year fellowship in pediatric neurology is now available from the Julian D. Levinson research foundation in conjunction with the children's division of the Cook County Hospital, Chicago; salary $3,500--communications should be sent to Dr. Abraham Levinson, Children's Division, Cook County Hospital, Chicago 12.... A new publication, "Epilepsy News", published by the Epilepsy Association of New York (Dr. Harry Sands, executive director), has appeared (October 1953)....

Percy Bailey

REVIEW COURSES IN BASIC and CLINICAL NEUROLOGY

APRIL 26, 27, 28, 1954

Preceding the

1954 AMERICAN ACADEMY OF NEUROLOGY MEETING

Shoreham Hotel, Washington, D. C.

THE HYPOTHALAMIC REGION—April 26, 1954. Dr. A. L. Sahs, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROPATHOLOGY—April 26, 1954. Dr. Fae Y. Tichy, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00. Deposit on Loan Box: $25.00.

COMA—April 27, 1954. Dr. Joe R. Brown, chairman. Fees: Juniors. $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

DISEASES OF THE SPINAL CORD—April 27, 1954. Dr. Benjamin Boshes, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROPHYSIOLOGY—April 27-28, 1954. Dr. J. L. O'Leary, chairman. Fees: Juniors: $15.00; Fellows, Actives and Associates: $20.00; Non-members: $25.00.

THE REFLEXES—April 28, 1954, A.M. Dr. Russell N. DeJong, chairman. Fees: Juniors: $5.00; Fellows, Active and Associates: $8.00; Non-members: $12.00.

HEADACHE—April 28, 1954, P.M. Dr. A. P. Friedman, chairman. Fees: Juniors: $5.00; Fellows, Actives and Associates: $8.00; Non-members: $12.00.

ENROLLMENT FOR ALL COURSES IS LIMITED

Priority will be determined by date of application

•

Outline of each course, application and further information may be obtained from

A. B. Baker, M.D., 19 Millard Hall, University of Minnesota

Minneapolis 14, Minnesota

Geriatrics — *a neurologic challenge*

One out of every three Americans is, or at any moment may become, a geriatric patient. More than 50,000,000 men and women are now over 45 years old.

Many of the problems which confront the neurologist today belong to the field of geriatric medicine. To round out the total clinical picture of your patient over 45, it is essential to keep abreast of the latest developments in geriatrics. For best and most complete coverage of this rapidly growing field, read GERIATRICS, the journal devoted to research and clinical study of the diseases and processes of aging.

Geriatrics *(a* LANCET *Publication)*
84 South Tenth Street, Minneapolis, Minnesota

POSTGRADUATE COURSE IN CLINICAL NEUROLOGY
University of Michigan Medical School — **Department of Postgraduate Medicine**
Ann Arbor, Michigan — **March 8, 9 and 10, 1954**

THIS course is designed to reorient the practicing physician in regard to the nervous system and the disease processes affecting it. The importance of the neurologic history and the procedure of the neurologic examination will be reviewed, with special emphasis on some of the newer diagnostic techniques as well as on ancillary methods of investigation and diagnosis. The close relationship between systemic disease and nervous system involvement or complications will be stressed, and many of the neurologic manifestations more commonly encountered in the general practice of medicine will be discussed individually. Diagnostic procedures, differential diagnosis and the newer modes of therapeutic approach will be presented. The course will be augmented by clinical presentations, motion picture demonstrations, and a review of the essential laboratory procedures.

Detailed program may be obtained from HOWARD H. CUMMINGS, M.D., Chairman, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Michigan

BALDPATE, Inc.

Geo. 2131 — **Georgetown, Mass.**

Located in the hills of Essex County, 30 miles north of Boston

For the treatment of
psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Psychotherapy is the basis of treatment;
electric shock treatments, sub-coma and deep coma insulin therapy when indicated;
sleep treatment for withdrawal of narcotics.

Occupation under a trained therapist, diversions and outdoor activities.

G. M. Schlomer, Medical Director

THE INSTITUTE FOR CHILD STUDY

2255 West Adams Blvd., Los Angeles 18, Calif.

Treatment center for the brain injured, slow-learning, or emotionally disturbed child.
Individualized program under strict medical and psychological supervision.
Ranch school for older children; small clinic school for younger children.
Official training school for the National Society For the Brain Injured.

For information write

P. O. Box 1377, Beverly Hills Station, Beverly Hills, California

for emotionally disturbed children . . . .

THE ANN ARBOR SCHOOL

. . . is a private school for children from six to fourteen, of average or superior intelligence, with emotional or behavior problems.

. . . providing intensive individual psychotherapy in a residential setting.

A. H. KAMBLY, M.D.
Director

411 First National Building
Ann Arbor, Michigan

FOUNDED 1879

RING SANATORIUM

Eight miles from Boston

For the study, care and treatment of emotional, mental, personality and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric, or neurological supervision.

Full resident and associate staff.

Benjamin Simon, M.D.
Director

Consultants in all specialties.

Charles E. White, M.D.
Assistant Director

Arlington Heights, Massachusetts
Telephone AR 5-0081

FRANCIS W. RUSSELL
Executive Secretary

Improved cerebral sedative

GENO SCOPOLAMINE IN PARKINSONISM

Prolonged sedation of psychic and motive centers is obtained without scopolamine's high toxicity or induced tolerance.

Sample and literature on request

LOBICA-DEBRUILLE, INC. | **1841 Broadway New York 23, N. Y.**

---

an active treatment *hospital*

for acute psychoses, psychoneurotic and personality disorders, senile and arterio-sclerotic problems, alcohol and drug addiction cases.

OFFNER and REITER machines for electro-coma administered by trained teams; insulin treatment – both full and sub-coma. Analytical and dynamically-oriented psychotherapy. Staff includes Diplomates, American Board of Neurology and Psychiatry; internist and associate physician; consultants in most specialties nearby; graduate nurses, trained attendants totalling 60 for full coverage of maximum 70 patients.

Proper segregation on 120 acre estate an hour from New York; variety of tasteful, comfortable accommodations with first-class cuisine, at realistic rates.

Hall-Brooke

Greens Farms, Box 31, Conn. : Westport 2-5105 : New York: Enterprise 6970
GEORGE K. PRATT, M.D., F.A.P.A., MEDICAL DIRECTOR
HEIDE F. JONES-BERNARD, ADMINISTRATOR

Lederle

Artane®

HYDROCHLORIDE

Trihexyphenidyl Hydrochloride *Lederle*

IN PARKINSONISM

POSTENCEPHALITIC • ARTERIOSCLEROTIC • IDIOPATHIC

ARTANE *Lederle* exerts an antispasmodic effect on muscle and inhibits parasympathetic nervous activity. Thus, muscle spasm is relaxed both directly and indirectly—a two-fold action especially valuable in the symptomatic relief of Parkinsonism of all three types.

ARTANE does not lose effectiveness with repeated use, and even when administered over long periods, exerts no deleterious action on bone marrow function.

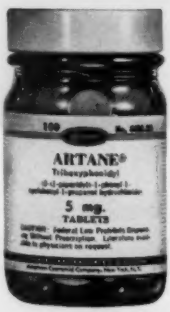
ARTANE is administered orally, in tablet or elixir form, three or four times daily. Dosage starts with 1 mg. the first day, gradually increased, according to response, to 6 mg. to 12 mg. daily.

ARTANE TABLETS are supplied in 2 mg. and 5 mg. strengths, in bottles of 100 and 1,000. ARTANE ELIXIR (2 mg. per teaspoonful [4 cc.]) is supplied in 16 fluid ounce bottles.

LEDERLE LABORATORIES DIVISION

AMERICAN Cyanamid COMPANY

30 Rockefeller Plaza, New York 20, N.Y.



Calm, Relaxed AND *Alert*

MEBARAL®

BRAND OF MEPHOBARBITAL

WINTHROP

for the hyperexcitability so often found in

- **hypertension**
- **hyperthyroidism**
- **convulsive disorders**
- **difficult menopause**
- **psychoneurosis**
- **hyperhidrosis**

Mebaral's soothing sedative effect is obtained without significantly clouding the patient's mental faculties.

Average Dose:

Adults—32 mg. to 0.1 Gm. (optimal 50 mg.), 3 or 4 times daily.

Children—16 to 32 mg., 3 or 4 times daily.

Tasteless tablets of 32 mg. (½ grain)
50 mg. (¾ grain)
0.1 Gm. (1½ grains)
0.2 Gm. (3 grains) scored.

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

WINTHROP-STEARNS INC. New York 18, N.Y. • Windsor, Ont.

Mebaral, trademark reg. U.S. Pat. Off.